Antiretroviral therapy and pregnancy outcome in HIV-infected women in the United Kingdom and Ireland

A thesis presented for the degree of Doctor of Philosophy

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Claire Louise Townsend

UCL Institute of Child Health

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Declaration

I, Claire Townsend, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

The aim of this thesis is to explore pregnancy and perinatal outcomes in diagnosed HIV-infected women receiving antiretroviral therapy (ART) in the UK (United Kingdom) and Ireland. Population-based surveillance data on HIV-infected pregnant women and their children is collected through the National Study of HIV in Pregnancy and Childhood (NSHPC), which includes information on over 8000 pregnancies delivered between 1990 and 2007. The majority of diagnosed infected women now take highly active antiretroviral therapy (HAART) in pregnancy, which reduces the risk of mother-to-child HIV transmission. However, there have been concerns over the potential for maternal and fetal adverse effects, with conflicting findings from European and American studies regarding the association between HAART and premature delivery.

In this thesis, trends over time in the demographic characteristics of HIV-infected pregnant women in the UK and Ireland are described, along with changes in the uptake of interventions for preventing mother-to-child transmission. Transmission rates are explored over a period when HAART was routinely available, and subgroups of women managed in the context of regularly updated national guidelines are compared with respect to their risk of transmission. Multivariable logistic regression models are used to assess the association between type of ART exposure in pregnancy and adverse outcomes including pre-eclampsia, prematurity, stillbirth, neonatal death and congenital abnormality. In addition, using data from the European Collaborative Study and the Pediatric Spectrum of HIV Disease project alongside the UK and Ireland data, the effects of differences in populations and methodologies (study design and analytical approach) on the observed association between HAART and premature delivery are investigated, and a pooled analysis of individual mother-child pairs is carried out. Finally, the risks and benefits of ART in terms of adverse pregnancy outcomes and mother-to-child transmission were jointly modelled using Monte Carlo simulation methods, to produce a risk-benefit ratio.

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Role of the researcher

The National Study of HIV in Pregnancy and Childhood (NSHPC) is an ongoing surveillance study, which I joined in 2003. Initially, my responsibilities revolved mainly around the day-to-day running of the study, but as time went on I became more involved in extracting and cleaning the data and working on specific analyses. I registered as a doctoral student in April 2005. In the same year, I applied for a three-year MRC Special Training Fellowship in Health Services and Health of the Public Research, which began in September 2006.

Details of responsibilities

Between 2003 and 2004, I was responsible for processing incoming paediatric and obstetric reports, and entering the obstetric data into the Access database. From 2005 to 2006, I focused on the obstetric data collection and took more responsibility for checking and monitoring data quality, and modifying questionnaires to include new questions and to improve response rates and data quality. I took the lead on all the analyses presented in this thesis; this included preparing and cleaning the data and carrying out the statistical analyses (mostly in Stata). The Monte Carlo analyses presented in Chapter 6 were carried out using the statistical package R and were developed with the help of Dr Mario Cortina Borja.

Between 2006 and 2007, I set up a collaborative project with colleagues from the European Collaborative Study and the Pediatric Spectrum of HIV Disease project in the United States, to explore reasons for the underlying differences in the association between antiretroviral therapy and prematurity in studies with different methodologies.

I am the first author on five original papers relating to this thesis and a letter of correspondence, all published in peer-reviewed academic journals. These are listed and reproduced in Appendix 1 (page 328). Conference abstracts arising from work included in this thesis are also listed in Appendix 1.

Acronyms and abbreviations

Studies and organisations

BHIVA	British HIV Association
BPSU	British Paediatric Surveillance Unit
CDC	(United States) Centers for Disease Control and Prevention
CHIVA	Children's HIV Association
ECS	European Collaborative Study
EUROCAT	European surveillance system for congenital anomalies
FDA	(United States) Food and Drug Administration
HPA	Health Protection Agency
HPS	Health Protection Scotland
ICH	Institute of Child Health
MRC	Medical Research Council
NSHPC	National Study of HIV in Pregnancy and Childhood
PSD	Pediatric Spectrum of HIV Disease project
UCL	University College London
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Other

AIDS	Acquired immune deficiency syndrome
AOR	Adjusted odds ratio
ART	Antiretroviral therapy
CD4 cell	Cluster of differentiation-4, T lymphocyte
CI	Confidence interval
df	Degrees of freedom
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IDU	Injecting drug use
IQR	Interquartile range
LRT	Likelihood ratio test
MTCT	Mother-to-child transmission
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NA	Not applicable
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
OR	Odds ratio
PCR	Polymerase chain reaction
PI	Protease inhibitor
UK	United Kingdom
US	United States of America

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I would like to begin with sincere thanks to my supervisors, Pat Tookey, Marie-Louise Newell and Mario Cortina Borja, who provided me with invaluable support, guidance, and encouragement throughout this project.

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I am grateful to all the clinicians and other health professionals who report to the National Study of HIV in Pregnancy and Childhood (NSHPC) and to Annemiek de Ruiter and Hermione Lyall for their collaboration.

Finally I would like to thank my friends and family, especially my parents for supporting me in so many ways throughout my academic career, and Mike for his patience, understanding and confidence.

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Chapter 1 Introduction

1.1 Global epidemiology of HIV

In the 25 years since the human immunodeficiency virus type-1 (HIV) was first identified, around 60 million people have been infected with the virus and at least 25 million have died (UNAIDS/WHO, 2007; Volberding *et al.*, 2008). In 2007 alone, an estimated 33 million people were living with HIV worldwide, including 15 million women and 2.5 million children. Western and Central Europe accounted for 760,000 of those individuals (UNAIDS/WHO, 2007), about a tenth (77,400) of whom were living in the United Kingdom (UK) (Health Protection Agency, 2008). Sub-Saharan Africa is by far the region most severely affected by the HIV pandemic, accounting for two thirds of all infections but only 10% of the world's population (Volberding *et al.*, 2008).

HIV is transmitted through contact with infected blood, for example through blood transfusions or sharing of contaminated needles, through sexual contact, and vertically from mother-to-child, during pregnancy, delivery or breastfeeding (Thorne & Newell, 2003). In the early years of the HIV epidemic most infections occurred in high risk groups such as injecting drug users and homosexual men. Although these groups continue to experience higher rates of transmission than the general population, the HIV pandemic today is driven mainly by heterosexual transmission (UNAIDS, 2008). There is, however, widespread regional variation in the relative importance of these transmission routes. In Africa, where the epidemic is more generalised, the vast majority of infections are acquired heterosexually, while in Asia, ongoing transmission is driven by injecting drug use as well as commercial sex

(UNAIDS, 2008). An increase in heterosexually-acquired infections in Western Europe, particularly in people originating from sub-Saharan Africa, has led to a corresponding increase in the proportion of new infections in women from 25% in 1995 to around 35% in 2006 (Hamers & Downs, 2004; Herida *et al.*, 2007). In the UK, about 55% of newly diagnosed infections in 2007 were in heterosexual men and women, over two thirds of whom were born in Africa (Health Protection Agency, 2008; The UK Collaborative Group for HIV and STI Surveillance, 2007). Paediatric HIV infection, acquired mainly through mother-to-child transmission (MTCT), accounts for only a small proportion of infections in Western Europe and other developed countries, thanks to effective prevention measures including antiretroviral therapy (ART), elective caesarean section delivery and avoidance of breastfeeding (Newell, 1998). In Africa, however, the absence of such measures means that over 400,000 children are infected with HIV each year (UNAIDS/WHO, 2007).

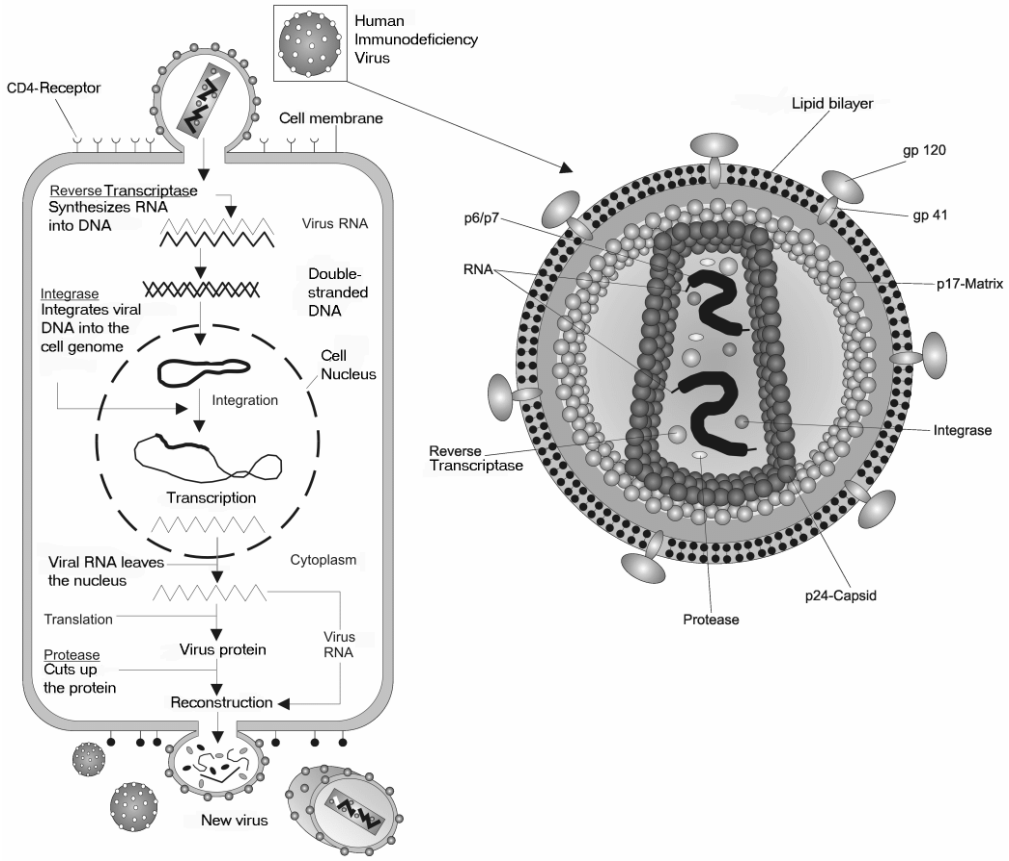
1.2 Biology of HIV infection and treatment

HIV is a blood-borne ribonucleic acid (RNA) retrovirus that targets the immune system. There are two main variants, HIV-1 (discussed here) and HIV-2; HIV-2 is believed to have arisen from a different primate reservoir, is less pathogenic, and is rarely found outside of Western Africa (Lemey *et al.*, 2003; Schim van der Loeff & Aaby, 1999). The HIV-1 epidemic is dominated by a number of subtypes, or clades, characterised by their geographic distribution: for example, subtype B accounts for most infections in Europe and the Americas, while subtype C dominates in southern Africa and South Asia (Osmanov *et al.*, 2002).

The HIV virus infects CD4+ T lymphocyte cells (CD4 cells) using CD4 receptors on the outside of the cell; after entry into the cell, the HIV RNA is transcribed into

deoxyribonucleic acid (DNA), which becomes integrated into the host genome (Figure 1.1) (Male *et al.*, 2006). The cell's internal processes are then used to transcribe new viral RNA strands and produce viral proteins, including reverse transcriptase, protease and integrase enzymes, which are important in the life cycle of the virus and are the targets of different antiretroviral drugs. These viral products are assembled into new virions, which are released from the cell and proceed to infect new cells. The number of viral particles in the blood (viral load) reflects the severity of infection and can be measured using standard tests, which detect the number of HIV RNA copies per milliliter of blood. Viral load is said to be undetectable if it falls below the detection limit of the laboratory assay, which has been reduced from 1000 copies/ml to 50 copies/ml with improvements in assays (Mulder *et al.*, 1994; Mulder *et al.*, 1997).

Figure 1.1 HIV life cycle and structure

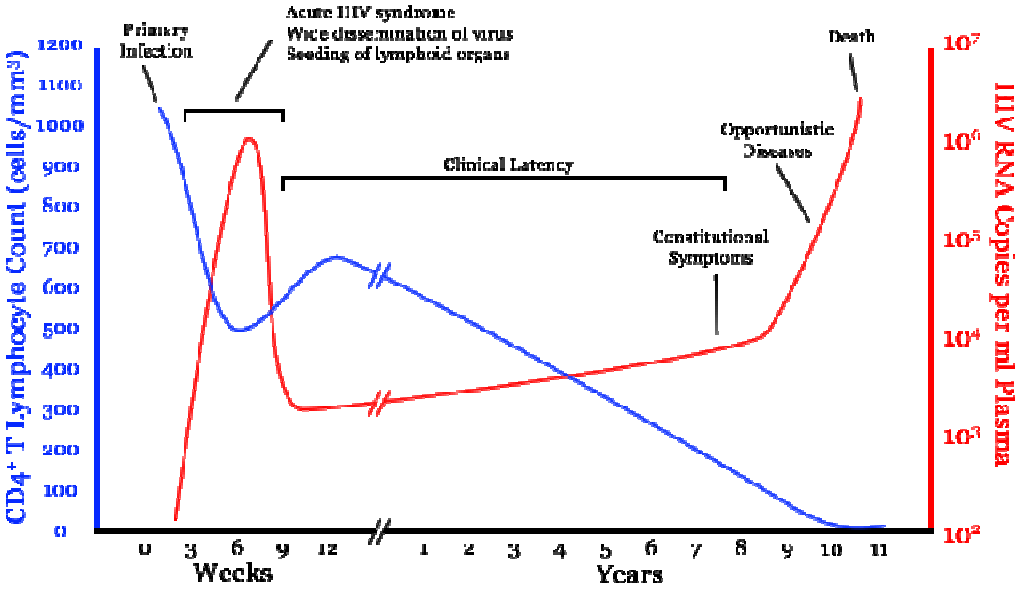


Source: http://en.wikipedia.org/wiki/HIV (Accessed 25 January 2009)

HIV impairs normal T lymphocyte function, eventually causing cell death, and infection is associated with a decline in CD4 cell levels in infected individuals (Figure 1.2). Primary infection is usually followed by a long and largely asymptomatic latent period (Figure 1.2). Median time from seroconversion to onset of symptoms is around 9 to 11 years and varies by age at infection and route of acquisition (Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action, 2000). In the absence of treatment, a gradual decline in CD4 cells occurs throughout this period (Figure 1.2), leaving the individual increasingly vulnerable to mild opportunistic infections. Progression to acquired immune deficiency syndrome (AIDS) usually occurs once CD4 counts fall

below 200 cells/µl, and is associated with a more serious risk of opportunistic infections and ultimately death (Male *et al.*, 2006).

Figure 1.2 Relationship between HIV copies (viral load) and CD4 counts over the average course of untreated HIV infection



Source: (Luzzi *et al.*, 2003), obtained from http://en.wikipedia.org/wiki/HIV (Accessed 25 January 2009).

Antiretroviral therapy

There are currently five main classes of antiretroviral drugs available, which target different stages of the HIV life cycle (Table 1.1). These drugs reduce viral replication and slow the onset of disease progression, but cannot completely clear the virus. The first three classes of antiretroviral drugs to be licensed were nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) in 1987, protease inhibitors (PIs) in 1995, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in 1996; entry inhibitors were added in 2003 and integrase inhibitors in 2007 (US Food and Drug Administration, 2008).

Table 1.1 Antiretroviral drugs

Class of drug	Activity / target	Examples
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Prevent reverse transcription by inhibiting the reverse transcriptase enzyme; can also be incorporated into new viral DNA, causing DNA chain termination.	zidovudine, lamivudine, abacavir, didanosine, stavudine, tenofovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Inhibit reverse transcription directly by binding to the reverse transcriptase enzyme and interfering with enzyme activity.	efavirenz, nevirapine
Protease inhibitors (PIs)	Inhibit the protease enzyme, which cleaves proteins for assembly into new viral particles.	nelfinavir, saquinavir, ritonavir, atazanavir, lopinavir
Integrase inhibitors	Inhibit the integrase enzyme, which is responsible for integration of the provirus into the host genome.	raltegravir
Fusion/entry inhibitors	Interfere with binding, fusion or entry of HIV to the host cell by binding to targets such as chemokine receptors.	enfuvirtide, maraviroc

(Volberding *et al.*, 2008; Weller & Williams, 2001)

Zidovudine was the first drug to be licensed for treatment of HIV, and in 1994 was recommended for use in pregnancy (Public Health Service Task Force, 1994). Treatment with zidovudine alone delays disease progression but the benefits are short-lived. A combination of two drugs provides more effective viral suppression, and treatment with three or more drugs, or highly active antiretroviral therapy (HAART), usually from at least two different classes, is now standard. HAART traditionally consisted of two NRTIs and either a PI or an NNRTI, although the availability of new drug classes is leading to a wider range of possible regimens. Because the different classes of drugs target different stages of viral replication, treatment with combination therapy reduces the risk of the virus developing resistance to a given drug class. Current treatment guidelines in Europe and the UK recommend starting HAART once CD4 counts fall below 350 cells/µl, or an AIDS-

defining condition is diagnosed (BHIVA, 2008; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2008).

1.3 HIV in pregnant women

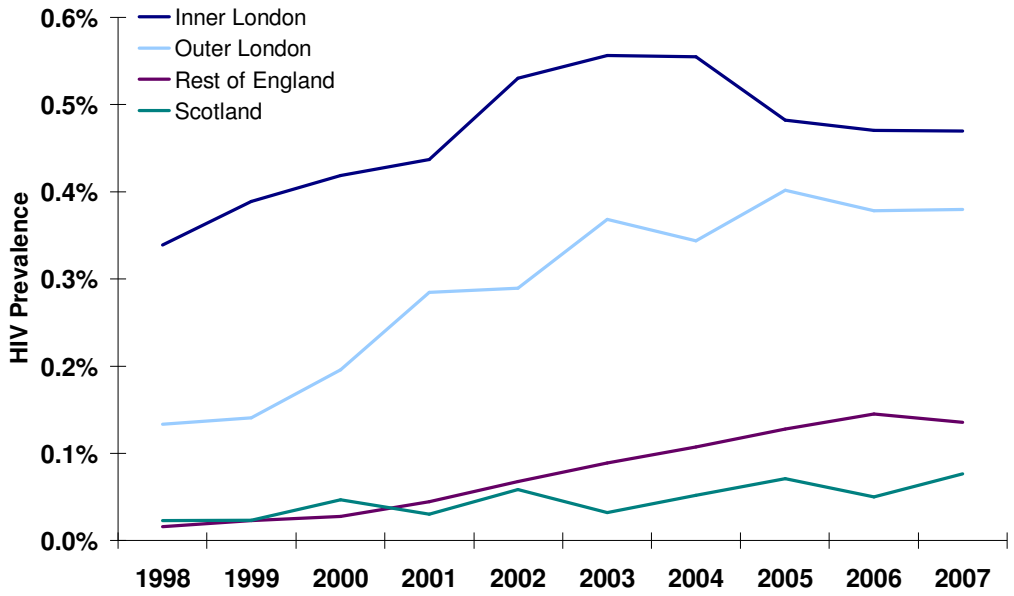
Antenatal prevalence

In the UK, unlinked anonymous surveillance of HIV in pregnant women is carried out using neonatal blood samples that are routinely collected for newborn metabolic screening tests (Ades *et al.*, 1991; Cortina-Borja *et al.*, 2004). Residual samples are tested for the presence of HIV antibody, which reflects HIV seroprevalence in the mother due to the passive transplacental passage of maternal antibody to the fetus during pregnancy. The unlinked anonymous survey began in 1988, and in 2007 covered 62% of births in England and Scotland, including London, the South East of England and most other metropolitan areas (Health Protection Agency, 2008; Nicoll *et al.*, 1998). Samples are linked with birth registration records using the child's date of birth and address, to obtain information on parental country of birth and area of residence; all personal identifiers are then permanently deleted ('unlinked') from laboratory records to preserve anonymity (Cortina-Borja *et al.*, 2004).

Unlinked anonymous surveys have shown a substantial rise in antenatal prevalence of HIV in the areas covered by the surveys over the last two decades. In London prevalence rose from 0.03% in 1988 to 0.19% in 1997 and 0.42% in 2006 (Nicoll *et al.*, 1998; The UK Collaborative Group for HIV and STI Surveillance, 2005; The UK Collaborative Group for HIV and STI Surveillance, 2007). In the rest of England, prevalence remained low throughout the 1990s, but rose from 0.02% in 1997 to 0.14% in 2006 (Figure 1.3) (The UK Collaborative Group for HIV and STI

Surveillance, 2007). The overall prevalence of HIV in women giving birth in England and Scotland more than doubled between 2000 and 2006 from 0.09% (about 1 in 1140 women) to 0.23% (1 in 440 women) (The UK Collaborative Group for HIV and STI Surveillance, 2005; The UK Collaborative Group for HIV and STI Surveillance, 2007). HIV prevalence in the UK is highest among women born in sub-Saharan Africa (2.1% in 2006) (Cortina-Borja *et al.*, 2004), although this is notably lower than prevalence rates in sub-Saharan Africa, which are over 5% in most countries, and over 25% in many southern African countries (UNAIDS, 2008). HIV prevalence in UK-born women is much lower, but increased significantly between 2000 and 2006, from 0.02% to 0.05% (The UK Collaborative Group for HIV and STI Surveillance, 2007).

Figure 1.3 HIV prevalence among pregnant women in England and Scotland by area of residence



Prevalence obtained from unlinked anonymous survey of newborn infant dried blood spots; includes diagnosed and undiagnosed women. Adapted from Figure 1, published on the Health Protection Agency website, 2008 (www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1203084355122#f1, accessed 25 January 2009).

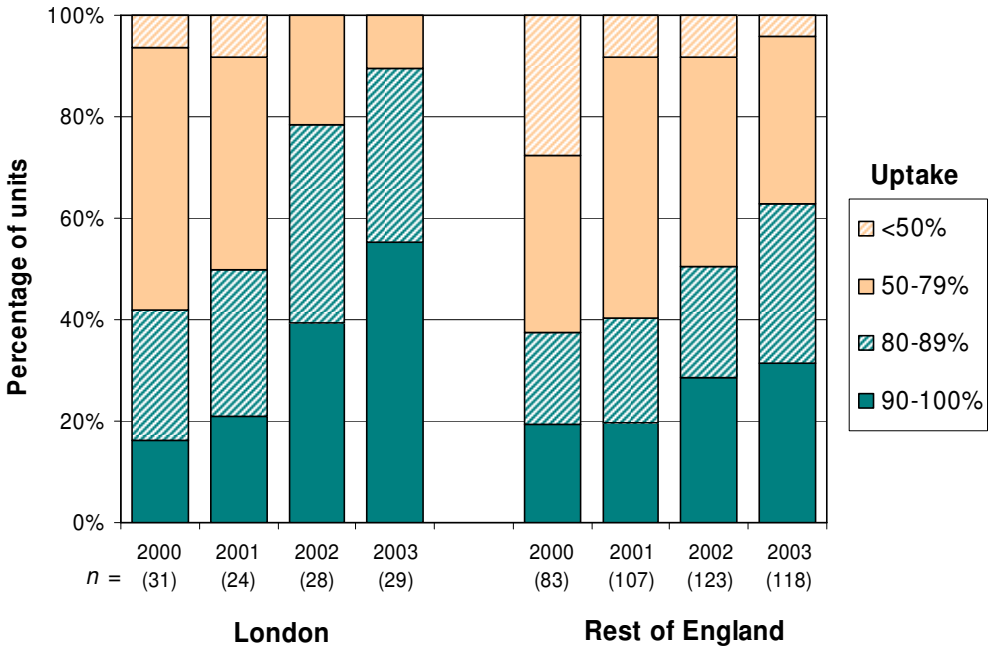
Antenatal testing and detection rates

In most resource-rich countries, including those in Western Europe, pregnant women are now routinely offered an HIV test during pregnancy (Deblonde, Claeys, & Temmerman, 2007). In England, the Department of Health introduced a policy of routine offer and recommendation of antenatal HIV testing in 1999, to be implemented by the end of 2000 (NHS Executive, 1999). At the time, most units only provided HIV testing on request or for selected groups of women perceived to be at higher risk, but this approach was largely ineffective (Nicoll *et al.*, 1998; Tookey *et al.*, 1998). A target of 90% uptake of testing was set for the end of 2002, with the aim of diagnosing 80% of HIV-infected pregnant women. A similar universal testing policy was implemented in Ireland around the same time (Health Protection Surveillance Centre, 2007), and Scotland, Wales and Northern Ireland followed in 2002 and 2003 (Communicable Disease Surveillance Centre Northern Ireland, 2003; National Institute for Clinical Excellence, 2003; Scottish Executive Health Department, 2002). Uptake of antenatal testing rose rapidly following the introduction of the policy, and by 2003 almost all London antenatal units and around 60% of units elsewhere in England were reporting over 80% uptake of testing (Figure 1.4) (Townsend, Cliffe, & Tookey, 2006).

The proportion of HIV-infected pregnant women diagnosed before delivery can be estimated by aligning unlinked anonymous seroprevalence data with cases of diagnosed HIV infection in pregnancy reported to the National Study of HIV in Pregnancy in Childhood (NSHPC). Although individual cases cannot be linked, the alignment provides an estimate of the proportion of women detected through antenatal screening at a regional level. Before 1997, less than 25% of HIV-infected pregnant women were diagnosed before they delivered (Nicoll *et al.*, 1998). By 1999 detection rates had already risen to around 60%, and since 2003, following the

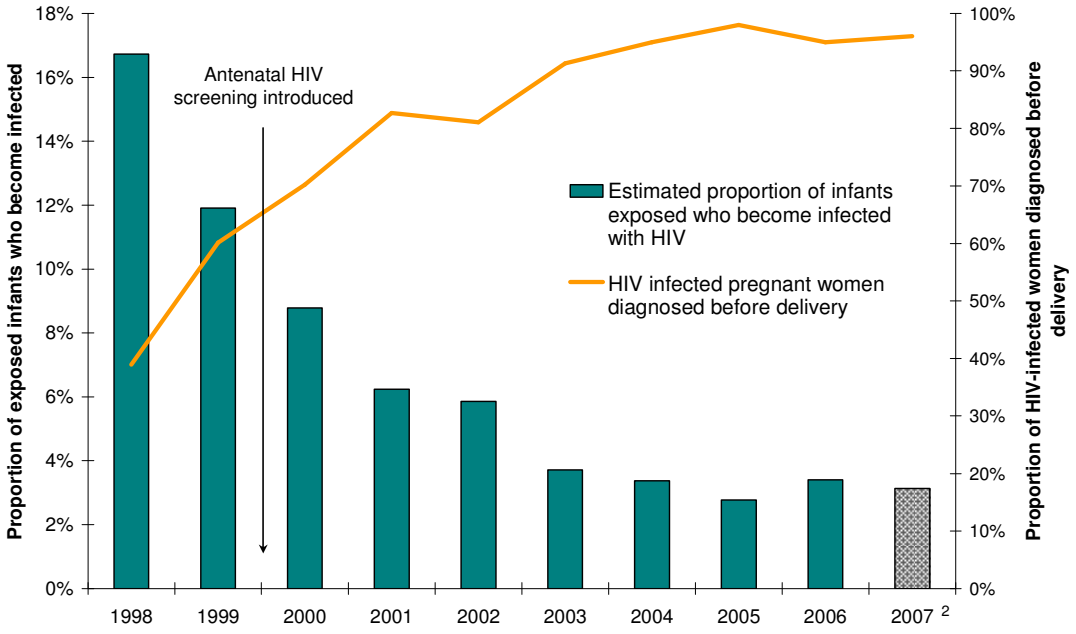
introduction of universal antenatal screening, rates of over 90% have been achieved (Figure 1.5) (The UK Collaborative Group for HIV and STI Surveillance, 2005; The UK Collaborative Group for HIV and STI Surveillance, 2007).

Figure 1.4 Uptake of antenatal HIV testing over time in London and elsewhere in England, among units in which the routine offer policy had been implemented and for which adequate data were provided



Adapted from: Townsend CL, Cliffe S, Tookey PA. Uptake of antenatal HIV testing in the United Kingdom: 2000-2003. *J Public Health (Oxf)* 2006; 28(3): 248-252. By permission of Oxford University Press.

Figure 1.5 Estimated proportion of HIV-infected pregnant women diagnosed before delivery and of exposed infants becoming infected with HIV[1], England & Scotland



[1] Assumes vertical transmission rate of 26.5% in undiagnosed women and 2.2% in diagnosed women
[2] Based on reports received by the end of June 2008, data for recent years is subject to reporting delay and detection rates will increase as further reports are received.

Adapted from Figure 5, published on the Health Protection Agency website, 2008 (www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1203084355122#f1, accessed 26 January 2009).

Pregnancy and HIV

Before ART became widely available, many diagnosed HIV-infected women would not have considered parenthood; prognosis and life expectancy were poor, and the risk of a child being infected was around 15-20% in Europe (Duong *et al.*, 1999; European Collaborative Study, 2001). HIV diagnosis was associated with a decline in pregnancy incidence and live birth rates (Stephenson & Griffioen, 1996; van Benthem *et al.*, 2000) and an increase in termination rates (van Benthem *et al.*, 2000). As well as altering reproductive decisions, HIV infection may also affect the ability to conceive or to carry a pregnancy to term. Lower conception rates and

increased pregnancy loss compared with uninfected controls have been reported in some cohorts of infected women in Africa, although not in all (Allen *et al.*, 1993; Gray *et al.*, 1998; Nebie *et al.*, 2001). Over the last decade, ART has led to dramatic reductions in morbidity and mortality, as well as in the risk of MTCT (European Collaborative Study, 2001; European Collaborative Study, 2005d; Mocroft *et al.*, 2003). Recent studies have shown that HIV-infected women are now more likely to desire children (Cliffe, 2005; Heard, Sitta, & Lert, 2007); there is also evidence that births to HIV-infected women have increased, and that fewer women are opting for terminations (European Collaborative Study, 2005b; Massad *et al.*, 2004; van Benthem *et al.*, 2000).

Pregnancy itself does not appear to adversely affect the course of HIV disease (European Collaborative Study and the Swiss HIV Pregnancy Cohort, 1997; Minkoff *et al.*, 2003; Saada *et al.*, 2000), nor does short-course treatment in pregnancy, either in terms of progression to AIDS or death, or in terms of changes in CD4 cell count or HIV RNA viral load levels (Bardeguez *et al.*, 2003; Martin *et al.*, 2006; Tungsiripat, Drechsler, & Aberg, 2007). Declines in CD4 count in pregnancy have been reported, but appear to be due to haemodilution, and tend to resolve after delivery (Saada *et al.*, 2000; Tuomala *et al.*, 1997). Although evidence is limited, there does not appear to be a detrimental effect of short-course HAART or zidovudine monotherapy in pregnancy on subsequent response to treatment (Martin *et al.*, 2006).

1.4 Mother-to-child transmission

Mechanisms, timing and rates

Mother-to-child transmission of HIV can take place in the antepartum, intrapartum and postpartum period and occurs through contact with infected maternal fluids and through breastfeeding (Newell, 1998). Although the placenta acts as an important barrier to HIV, *in utero* transmission can occur, probably as a result of transfusion of infected blood to the fetus through small tears in the placenta, or through placental disruption, for example by chorioamnionitis (Newell, 1998). Most perinatal HIV transmission occurs around the time of delivery, following exposure of the infant to maternal vaginal secretions and infected blood (Mofenson, 1997; Newell, 1998). Transmission also occurs postnatally through breastfeeding, which accounts for a third to half of perinatal infections in breastfeeding populations (Fowler & Newell, 2002). In an individual patient meta-analysis, the rate of postnatal transmission after four weeks of age was estimated to be 8.9 per 100 child-years of breastfeeding (The Breastfeeding and HIV International Transmission Study (BHITS) Group, 2004). In the absence of prophylactic interventions, MTCT rates for HIV are estimated to range from 13% to 32% in resource-rich countries and from 25% to 48% in resource-poor countries (Dabis *et al.*, 1993), with differences attributed mainly to variation in breastfeeding duration.

Factors shown to be associated with MTCT include maternal plasma HIV RNA viral load, CD4 count, mode of delivery, duration of ruptured membranes and gestational age at delivery (European Collaborative Study, 1996b; Stratton *et al.*, 1999; Thorne & Newell, 2004b). HIV RNA viral load is the strongest predictor of MTCT, with a doubling of risk for each $\log_{10}$ increase in viral load (Cooper *et al.*, 2002; European

Collaborative Study, 1999). Low CD4 count is also associated with an increased risk of transmission (European Collaborative Study, 1996b; European Collaborative Study, 2001). Differences in transmission by mode of delivery were first detected in observational studies in the early 1990s, in which elective caesarean section was found to be associated with a reduced risk of transmission compared with vaginal delivery (European Collaborative Study, 1994; European Collaborative Study, 1999; Moodley *et al.*, 1994). This was confirmed in both a randomised clinical trial and a meta-analysis, which demonstrated a more than 50% reduction in transmission associated with planned pre-labour caesarean section (The European Mode of Delivery Collaboration, 1999; The International Perinatal HIV Group, 1999). In a meta-analysis, which included mostly untreated women, duration of ruptured membranes was associated with a 2% increase in transmission for each additional hour of ruptured membranes (The International Perinatal HIV Group, 2001). Prematurity was found to be a risk factor for transmission in early studies of women who were mostly untreated or on zidovudine alone (European Collaborative Study, 1996b; European Collaborative Study, 1999; Kuhn *et al.*, 1999). However, it is less clear whether premature delivery remains an independent predictor of transmission in HAART-treated women, particularly if viral load is suppressed (European Collaborative Study, 2005d; Warszawski *et al.*, 2008).

The primary intervention for reducing MTCT is ART, which is administered to the mother during pregnancy and delivery to reduce plasma HIV RNA viral load, and to the neonate as prophylaxis (Newell & Thorne, 2004). Elective caesarean section delivery and formula feeding are also now standard practice in resource-rich settings (BHIVA/CHIVA, 2008). This combined prevention approach led to overall declines in MTCT rates in resource-rich countries from around 20-25% to around 1-2% in the

late 1990s (Centers for Disease Control and Prevention, 2006; Cooper *et al.*, 2002; Duong *et al.*, 1999; European Collaborative Study, 2001), and rates of 1% or less have been reported in recent years (Dorenbaum *et al.*, 2002; European Collaborative Study, 2005d; Peters *et al.*, 2008; Warszawski *et al.*, 2008). Widespread use of HAART has meant that the majority of women achieve low or undetectable HIV RNA viral load by the time of delivery, and it is now unclear whether planned caesarean section delivery confers any additional benefit for these women. Elective caesarean section may carry a higher risk of postpartum morbidity than vaginal delivery (Read & Newell, 2005), although possibly not in women on HAART (Duarte *et al.*, 2006). Since 2005, guidelines have suggested that women on HAART who have uncomplicated pregnancies and an undetectable viral load may attempt a vaginal delivery, although there was limited evidence to support this recommendation. There is also uncertainty about the role of obstetric factors, such as duration of ruptured membranes and premature delivery, in relation to the risk of MTCT among women achieving viral suppression (European Collaborative Study, 2005d; Jamieson *et al.*, 2007; Newell & Thorne, 2004).

Antiretroviral therapy in pregnancy

In 1994, the beneficial effects of zidovudine in pregnancy were first demonstrated in the AIDS Clinical Trial Group (ACTG) 076 trial of women with CD4 counts above 200 cells/μl, in which zidovudine was administered antenatally, starting between 14 and 34 weeks gestation (median 28 weeks), intravenously in labour, and orally to the baby for the first six weeks of life (Connor *et al.*, 1994). The transmission rate was two thirds lower in the intervention (8%) than in the control arm (25%). The benefits of zidovudine have also been demonstrated in a number of observational studies in

non-breastfeeding populations (Cooper *et al.*, 2002; European Collaborative Study, 2001; Kind *et al.*, 1998; Mayaux *et al.*, 1997). Subsequently, the addition of lamivudine, another NRTI, to the 076 protocol was shown to further reduce the transmission rate to 1.6% in the Agence Nationale de Recherche sur le Sida (ANRS) 075 trial, but this was overshadowed by concerns about adverse events and drug resistance (Mandelbrot *et al.*, 2001). There have been no clinical trials of HAART in pregnancy, partly due to the low transmission rates (<2%) achieved with combination therapy (Dorenbaum *et al.*, 2002), but it has been shown in observational studies to have a greater effect on transmission rates than zidovudine alone. In the Women and Infants Transmission Study of around 1500 women in the United States (US), MTCT occurred in 10% of those taking zidovudine, 4% of those receiving dual therapy, and 1.2% of those on HAART (Cooper *et al.*, 2002). In developed countries, HAART is now the standard of care for treatment in pregnancy, with transmission rates around 1% (European Collaborative Study, 2005d; Warszawski *et al.*, 2008).

In recent years, a substantial proportion of women have been conceiving on HAART (European Collaborative Study, 2005a; Watts *et al.*, 2007). Current recommendations suggest that normal treatment should be continued after conception, with the exception of efavirenz (see page 42) (BHIVA/CHIVA, 2008; Perinatal HIV Guidelines Working Group, 2008). The majority of women diagnosed for the first time in pregnancy initiate treatment during the second or third trimester of pregnancy. Some women may already have depleted CD4 cell counts at diagnosis and require HAART for their own health, but for those diagnosed at an earlier stage of disease and initiating treatment purely for MTCT prophylaxis, less potent treatment options may be considered. Although zidovudine monotherapy is no longer

used for treatment of HIV-infected adults or children, it remains an option for MTCT prevention. Early studies suggested that when used in combination with elective caesarean section and no breastfeeding, zidovudine could reduce the risk of MTCT to below 1% (European Mode of Delivery Collaboration, 1999). The British HIV Association (BHIVA) Guidelines currently support this strategy for women who do not need HAART for their own health, have a pre-treatment viral load below 6000-10,000 copies/ml and are willing to deliver by planned pre-labour caesarean section (BHIVA/CHIVA, 2008). Recommendations in the US are more cautious, suggesting that zidovudine monotherapy should only be considered in women with viral load <1000 copies/ml (Perinatal HIV Guidelines Working Group, 2008). There are limited data on the selective use of zidovudine monotherapy for preventing MTCT in women who do not require HAART, and no trials have addressed the relative efficacy of this approach compared with short-course HAART. In an audit that included 85 women who received zidovudine monotherapy in pregnancy, only a quarter had started HAART following pregnancy (at a median of 28 months follow-up), and they were just as likely to have responded to treatment as those who had received short-course HAART (Martin *et al.*, 2006).

1.5 Safety and toxicity of antiretroviral therapy

Despite the clear benefits of ART, a number of side effects can occur, including nausea, vomiting, diarrhoea and rash, as well as a range of metabolic toxicities (Herman & Easterbrook, 2001). Lipodystrophy, or wasting of peripheral fat, is one of the more common symptoms experienced by patients on antiretroviral drugs (Carr *et al.*, 1998). More serious, acute toxicities can also occur: use of NRTIs can cause mitochondrial toxicity and has been shown to be associated with hyperlactataemia

(Brinkman *et al.*, 1998; Gerard *et al.*, 2000). In severe cases, toxicity can result in lactic acidosis, multi-organ failure and death. A number of reports of lactic acidosis in pregnant women have emerged, with several deaths (Luzzati *et al.*, 1999; Mandelbrot *et al.*, 2003; Sarner & Fakoya, 2002), and in 2001 the FDA issued a warning against the use of stavudine and didanosine in pregnancy; guidelines now recommend avoiding these drugs when pregnant (BHIVA/CHIVA, 2008; Coll *et al.*, 2002; Perinatal HIV Guidelines Working Group, 2008).

Nevirapine, an NNRTI, was commonly used in first-line therapy along with zidovudine and lamivudine, but there is now growing evidence linking this drug to an increased risk of hepatotoxicity in adults, particularly women and those with CD4 counts over 250 cells/µl (Baylor & Johann-Liang, 2004; Mazhude *et al.*, 2002). Symptoms usually appear in the first few weeks of treatment and include hepatitis, liver failure and rash. In severe cases nevirapine exposure can cause Stevens-Johnson syndrome, a hypersensitivity reaction affecting the skin; a number of such cases, including several deaths, have been reported in pregnant women (Hitti *et al.*, 2004; Joao *et al.*, 2006; Lyons *et al.*, 2003; Marazzi *et al.*, 2006). Because the risk of hepatotoxicity is associated with less advanced immunosuppression, nevirapine is no longer recommended for pregnant women with CD4 counts above 250 cells/µl (BHIVA/CHIVA, 2008; Coll *et al.*, 2002; Perinatal HIV Guidelines Working Group, 2008).

Prematurity

Concerns about high rates of premature delivery in women on combination therapy were first raised in 1998 in a small Swiss study (Lorenzi *et al.*, 1998). Since then, several other studies have reported similar findings (Boer *et al.*, 2007; European

Collaborative Study, 2004a; Grosch-Woerner *et al.*, 2008). It has been suggested that by reversing the immunological decline associated with HIV infection, ART could potentially be detrimental to the maintenance of pregnancy, which requires suppression of the pro-inflammatory component of the immune system (Fiore *et al.*, 2006). Nevertheless, several large-scale studies, mostly in the US, have failed to detect an association between ART and prematurity (Tuomala *et al.*, 2002; Tuomala *et al.*, 2005). Reasons for these conflicting findings remain unclear, but could relate to the limitations of observational data, including the inability to adjust for other risk factors for preterm delivery, the prevalence of which may differ between studies (Newell *et al.*, 2007), and bias in treatment allocation (Tuomala & Yawetz, 2006).

Studies in Europe

Following the initial report from Switzerland, the association between ART and prematurity was confirmed first in a combined analysis of the European Collaborative Study (ECS) and the Swiss study, and subsequently in an updated ECS analysis, which showed a two-fold increase in prematurity among 1075 women on HAART compared with 704 women on monotherapy or dual therapy (European Collaborative Study, 2004a; European Collaborative Study and the Swiss Mother + Child HIV Cohort Study, 2000). Some smaller studies reported a lack of association between treatment and prematurity, probably due to methodological differences (Bucceri *et al.*, 2002; Mandelbrot *et al.*, 2001). More recently, a significant association between HAART and prematurity has been reported from Germany, the Netherlands and the UK (Boer *et al.*, 2007; Grosch-Woerner *et al.*, 2008; Martin & Taylor, 2007).

Studies in the United States

Reports from the US have been conflicting, with initial reports suggesting no adverse effect of ART on timing of delivery. In an analysis of two clinical trials and five observational studies, prematurity rates were 15% in 533 women on combination therapy and 16% in 1590 women on monotherapy (Tuomala *et al.*, 2002). This study did show a 3.5-fold increased risk of very low birth weight (<1500 g) associated with PI-containing combination therapy. A more recent analysis based on the Women and Infants Transmission Study in the US also reported a lack of association between ART and prematurity (Tuomala *et al.*, 2005). However, in two other US studies, preterm delivery was significantly associated with PI-containing therapy (Cotter *et al.*, 2006; Schulte *et al.*, 2007).

Other studies

Few studies from outside Europe and the US have addressed the issue of ART and prematurity. In a South American study of 681 ART-treated women, unadjusted prematurity rates were 1.5 times higher in women on PI-based HAART compared with monotherapy or dual therapy, but the association was not significant (95% confidence interval [CI]: 0.6-3.4), possibly due to the small number of women on mono/dual therapy (*n*=94) (Szyld *et al.*, 2006). Recently, published findings from a study of over 300 pregnant women in Côte d'Ivoire, showed over a two-fold increase in low birth weight (<2500 g) associated with HAART in pregnancy, compared with zidovudine alone or in combination with lamivudine (Ekouevi *et al.*, 2008). Although gestational age was not available, and low birth weight was taken as a proxy, the association is likely due to prematurity.

In an attempt to inform the debate about ART and prematurity, a meta-analysis was carried out by Kourtis and colleagues (Kourtis *et al.*, 2007). Seven studies were

included in the comparison of combination therapy and monotherapy, and the authors concluded that there was no association with prematurity. However, they also found that longer duration of treatment and regimens that included a PI might increase the risk of prematurity. A significant degree of heterogeneity was noted between the studies, and questions remain about the appropriateness of merging the results (Patel, Thorne, & Newell, 2007).

Other obstetric outcomes

Pre-eclampsia

There is some evidence that pre-eclampsia is less common in HIV-infected than uninfected women, probably because HIV suppresses the inflammatory responses which contribute to the pathology of pre-eclampsia (Hall, 2007; Stratton *et al.*, 1999). However, two studies have suggested that the use of HAART may reverse this effect: results from a cohort study of 214 women seen in two London hospitals demonstrated a significantly increased risk of pre-eclampsia among women on HAART (8/76) compared with untreated women (0/61) (Wimalasundera *et al.*, 2002). In another study, a sharp increase in cases of pre-eclampsia was reported for 2001 to 2003, compared with data from 1985 to 2000, which the authors attributed to the increased use of HAART prior to pregnancy; women who were on HAART at conception were almost nine times more likely to develop pre-eclampsia than those who were not (Suy *et al.*, 2006).

Gestational diabetes

Concerns about gestational diabetes have also been raised. Impaired glucose tolerance was reported in 8% of ART-treated women in a small retrospective study

(Chmait *et al.*, 2002). A significant link between PIs and gestational diabetes was detected in the Pediatric AIDS Clinical Trials Group (PACTG) 316 trial, with rates of 4.6% in women on PIs compared with 1.7% in those not on PIs (Watts *et al.*, 2004a), and an increase over time in hospitalisations for gestational diabetes in HIV-infected pregnant women in the US has also been reported (Kourtis *et al.*, 2006). However, in two recent studies that explored the use of PIs and glucose intolerance, no association was detected (Hitti *et al.*, 2007; Tang *et al.*, 2006).

Stillbirth

In light of the proposed mechanisms underlying the association between ART and both pre-eclampsia and premature delivery, an increase in the risk of stillbirth might also be expected, particularly since pre-eclampsia is associated with an increased risk of fetal death (Sibai, Dekker, & Kupferminc, 2005). However, few studies have been large enough to investigate this association. In the study by Suy and colleagues described above, fetal death rates increased over time and were seven-fold higher in women on HAART before pregnancy than in those starting during pregnancy (Suy *et al.*, 2006). No association between ART and stillbirth has been reported in any other study, although in all cases the number of stillbirths was small (Ekouevi *et al.*, 2008; Tuomala *et al.*, 2002; Tuomala *et al.*, 2005; Watts *et al.*, 2004a).

Congenital abnormalities

Animal studies have provided limited evidence for a teratogenic effect of antiretroviral drug exposure in pregnancy. In monkeys, spinal malformations have been observed in fetuses exposed to efavirenz (Nightingale, 1998); spinal anomalies in human infants exposed *in utero* have also been reported (De Santis *et al.*, 2002;

Fundaro *et al.*, 2002), and efavirenz is now contra-indicated in early pregnancy (BHIVA/CHIVA, 2008; Perinatal HIV Guidelines Working Group, 2008).

Large-scale epidemiological studies have not shown any overall increase in abnormality rates associated with first trimester ART exposure (European Collaborative Study, 2005a; Watts *et al.*, 2007), nor have other smaller European cohorts (Bucceri *et al.*, 2002; Mandelbrot *et al.*, 2001). In addition, the Antiretroviral Pregnancy Registry (APR), an international prospective monitoring system based in the US, has reported no increased risk of birth defects associated with exposures to several individual drugs with numbers large enough to detect a 1.5-fold (zidovudine and lamivudine) or two-fold (abacavir, efavirenz, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir) increase in risk (Antiretroviral Pregnancy Registry Steering Committee, 2008; Covington *et al.*, 2004; Watts *et al.*, 2004b). However, an increased prevalence of abnormalities (4.5%, 95% CI: 2.6-7.3%) was recently detected in 266 infants exposed to didanosine, compared with a population rate of 2.7% (Antiretroviral Pregnancy Registry Steering Committee, 2008). An increased rate of genital abnormalities (hypospadias) associated with first trimester antiretroviral exposure has also been reported (7 of 382 male infants, versus 2 of 892 unexposed infants) (Watts *et al.*, 2007); these findings have yet to be confirmed in other studies, and further investigation is required. Concerns were also raised in relation to combined exposure to ART and folate antagonists following a report from a retrospective multi-centre study in London (Jungmann *et al.*, 2001), but the study included only nine infants with congenital abnormalities, and to date no other studies have raised similar concerns.

Other paediatric outcomes

Exposure to antiretroviral drugs has been shown to produce short- to medium-term changes in haematological parameters in exposed infants, including anaemia and reductions in platelets, neutrophils and lymphocytes (Connor *et al.*, 1994; Le Chenadec *et al.*, 2003; Sperling *et al.*, 1998). Reduced neutrophil and CD8+ lymphocyte counts have been shown to persist to at least eight years of age (European Collaborative Study, 2004b; European Collaborative Study, 2005c). However, the clinical significance of these observations is unclear; in a small study involving 16 children, no clinical symptoms were reported despite moderate-to-severe toxicity based on absolute neutrophil counts (Bunders, Thorne, & Newell, 2005).

A high incidence of mitochondrial dysfunction has been reported in a cohort of ART-exposed children in France (Barret *et al.*, 2003; Blanche *et al.*, 1999), and other cases have been reported from Italy and Spain (Noguera *et al.*, 2003; Tovo *et al.*, 2005). However, several studies in Europe and the US have failed to detect an increase in deaths in uninfected ART-exposed children (Bulterys *et al.*, 2000; Dominguez *et al.*, 2000; European Collaborative Study, 2003; Lindegren *et al.*, 2000; The Perinatal Safety Review Working Group, 2000). Although there is evidence from umbilical cord blood that mitochondrial damage can occur following exposure to ART *in utero* (Divi *et al.*, 2004; Divi *et al.*, 2007; Shiramizu *et al.*, 2003), the actual risk of long-term neurological disease remains unclear.

Studies in animals and using human cord blood have also demonstrated the potential for genotoxic and carcinogenic effects of *in utero* ART exposure (Olivero *et al.*, 1997; Olivero *et al.*, 1999; Olivero *et al.*, 2002). Epidemiological studies have so far detected no increase in tumour incidence in children exposed to ART, with median

age at last follow-up ranging from two to four years (Culnane *et al.*, 1999; European Collaborative Study, 2003; Hankin *et al.*, 2007; Hanson *et al.*, 1999). However, the potential for an increased risk of malignancies in later childhood or adulthood cannot be excluded.

1.6 Rationale for this thesis and overview

In the UK and Ireland, surveillance of HIV infection in pregnant women and children is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC). Through this unique surveillance system, information is collected prospectively on all pregnancies in HIV-infected women, and children are followed up through paediatricians to establish their infection status. Chapter 2 of this thesis provides an overview of the NSHPC and its methodology, and describes the other data sources used in this thesis.

Although the various risk factors for MTCT were well described in the mid- to late 1990s, HAART is now widely used in pregnancy and it is unclear whether factors such as vaginal delivery and prematurity remain associated with transmission in women with low or undetectable HIV RNA viral load. Furthermore, the impact of different strategies to prevent MTCT – for example, zidovudine monotherapy combined with elective caesarean section, or HAART combined with vaginal delivery – has not been investigated at a population level. The first part of Chapter 3 covers the epidemiology of HIV in pregnant women in the UK and Ireland since 1990, and in the second part of the chapter, MTCT rates are explored among women reported since 2000.

Data collected through the NSHPC has also enabled adverse effects associated with treatment to be monitored. Questionnaires are routinely updated to address pertinent issues; for example, because of concerns raised about HAART and pre-eclampsia, information on pregnancy complications has been collected since 2004. These findings are reported in Chapter 4, along with an analysis of first trimester exposure

to ART and the risk of congenital abnormalities. Because of the large number of HIV-affected pregnancies reported in the UK and Ireland, and the fact that data are collected prospectively through two parallel systems (obstetric and paediatric), some of the limitations encountered in smaller studies or passive reporting systems are avoided. In the first part of Chapter 5, the association between HAART and prematurity is explored using NSHPC data. The aim of the second part of the chapter is to investigate the reasons for conflicting findings with regard to ART and prematurity, by comparing three studies with different methodologies, including one based in the US.

Finally, in Chapter 6, Monte Carlo simulation models are used to compare the risks and benefits of ART in terms of pregnancy outcome and MTCT, and to quantify the ratio of risks to benefits for different treatment scenarios. Chapter 7 concludes with a full discussion of the findings, including their implications for policy and for future work in this field.

Areas not addressed in this thesis

Since no further information on HIV-infected women is collected through the NSHPC after delivery, this thesis could not address the impact of pregnancy or short-course treatment on postpartum HIV disease progression. Uninfected children are not routinely followed up once their infection status is established, so it was not possible to investigate the potential consequences of *in utero* ART exposure for exposed children. Follow-up of uninfected exposed children reported to the NSHPC was carried out between 2002 and 2005 in the CHART (CHildren exposed to Antiretroviral Therapy) study by Hankin and colleagues (Hankin, 2006; Hankin *et al.*, 2009).

1.7 Key Points

- Antiretroviral therapy is widely used for effective treatment of HIV disease, and for prevention of mother-to-child transmission (MTCT).
- Prevalence of HIV in women giving birth in England and Scotland has increased significantly in recent years, rising from 0.09% in 2000 to 0.23% in 2006.
- In the UK and Ireland, pregnant women are routinely offered an antenatal HIV test, and over 90% of infected women are now diagnosed by the time of delivery.
- MTCT can occur during pregnancy, at delivery and through breastfeeding, and is associated with high maternal HIV RNA viral load, CD4 cell count, duration of ruptured membranes and premature delivery.
- The risk of MTCT can be reduced with antiretroviral therapy, elective caesarean section delivery and formula feeding; these interventions have led to a decline in rates of MTCT in resource-rich countries from around 20-25% in the early 1990s to 1-2% in recent years.
- Most women now receive HAART in pregnancy and achieve low or undetectable HIV RNA viral load by the time of delivery. In this context, the contribution of other interventions and factors such as mode of delivery, duration of ruptured membranes and prematurity to MTCT risk has become less clear in recent years.
- ART is associated with a number of adverse effects; in some studies, an association between HAART in pregnancy and preterm delivery has been reported.
- Animal studies have suggested a potential risk of congenital abnormalities associated with ART exposure in early pregnancy, but so far no increased risk of

abnormalities has been detected in large-scale observational studies of children exposed to ART *in utero*.

- Other adverse effects reported in ART-treated pregnant women include pre-eclampsia, gestational diabetes, lactic acidosis, nevirapine-associated hepatotoxicity, and fetal death.
- Quantifying the risk of HAART in relation to the benefits in an important step in better understanding the relationship between ART and adverse events, and in improving the management of HIV in pregnancy.

Chapter 2 Aims and methods

2.1 Aim and objectives

Aim

To explore the association between antiretroviral therapy (ART) and pregnancy outcome in HIV-infected women in the UK and Ireland.

Objectives

1. To describe changes in the epidemiology of HIV in pregnant women over time, and estimate mother-to-child transmission rates according to risk factors and uptake of interventions.

2. To explore the association between ART and pregnancy and perinatal outcomes (pre-eclampsia, prematurity, birth weight, perinatal death, congenital abnormalities), allowing for maternal characteristics.

3. To explore differences in the association between ART and premature delivery in three observational studies (the National Study of HIV in Pregnancy and Childhood, the European Collaborative Study, and the Pediatric Spectrum of HIV Disease project), and to investigate the importance of methodology and analytical approach in explaining these differences.

4. To model the risks and benefits of ART in terms of adverse pregnancy outcomes and mother-to-child transmission, using Monte Carlo simulation methods.

2.2 Data sources

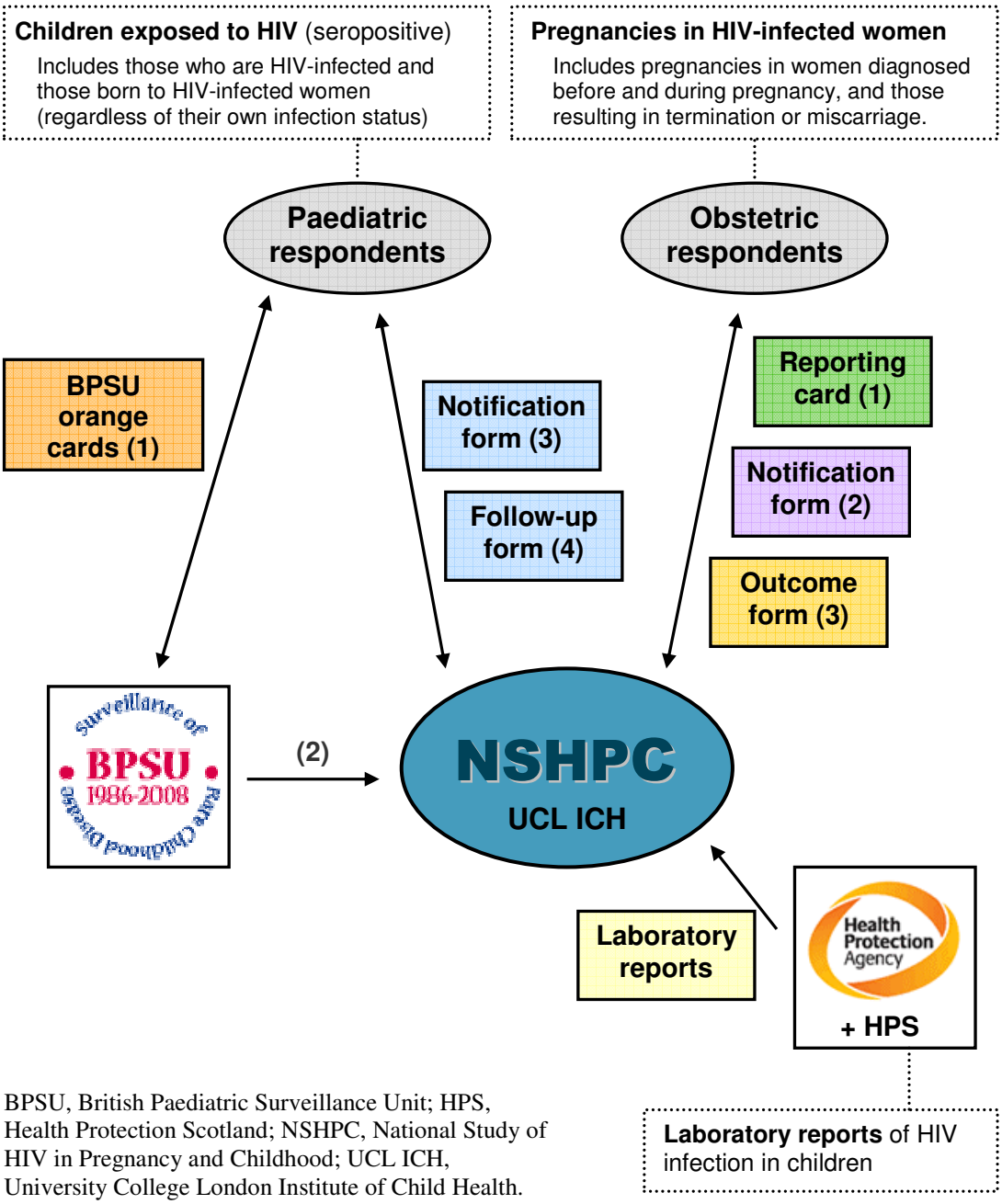
The National Study of HIV in Pregnancy and Childhood

Surveillance of HIV and AIDS in pregnant women and children in the UK and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC) (www.nshpc.ucl.ac.uk), based at the University College London (UCL) Institute of Child Health. The surveillance study relies mainly on two parallel, confidential reporting schemes, which aim to capture all diagnosed HIV-infected pregnant women accessing antenatal care, all HIV-infected children, and all infants born to infected women regardless of their own infection status (Figure 2.1).

Obstetric scheme

Obstetric HIV surveillance began in 1989 and is run under the auspices of the Royal College of Obstetricians and Gynaecologists (RCOG). Designated respondents (mostly midwives, obstetricians or genito-urinary physicians) responsible for all maternity units (*n* ~240) in the UK and Ireland are contacted quarterly and asked to report all pregnancies in HIV-infected women, regardless of the timing of HIV diagnosis or pregnancy outcome, using a standard reporting card (Appendix 2, page 371). The surveillance scheme is active, meaning that a response is required even if no cases are seen, and response rates of 93-96% are achieved (Table 2.1). Data on each reported pregnancy are collected using a notification form (Appendix 2, page 372) completed by the respondent. For pregnancies due to continue to term, a follow-up form is sent near the time of delivery (Appendix 2, page 373). No names are collected, but obstetric reports are linked to previous pregnancies and paediatric reports using dates of birth and demographic details, and duplicates are excluded. Questionnaires are reviewed and updated periodically.

Figure 2.1 Overview of NSHPC surveillance scheme



BPSU, British Paediatric Surveillance Unit; HPS, Health Protection Scotland; NSHPC, National Study of HIV in Pregnancy and Childhood; UCL ICH, University College London Institute of Child Health.

Table 2.1 Pregnancies in HIV-infected women: reports made by December 2008 through the obstetric reporting scheme

Reporting period	Response rate (%) *	Number of confirmed cases	Not yet confirmed **
1989 - 1999	94-96	1360	0
2000 - 2002	95-96	2031	0
2003	93	1066	28
2004	93	1277	39
2005	93	1239	89
2006	94	1355	103
2007	96	1390	149
Jan - Mar 2008	94	325	55
Apr - Jun 2008	91	304	100
Jul - Sep 2008	80	193	148

* Response rate for return of initial reporting card.
** Number of cases reported on initial card, but not confirmed by return of notification form.

N.B. Response rates for the last two quarters are likely to increase as late reports are received. Updated tables appear quarterly on the NSHPC website: www.nshpc.ucl.ac.uk ('Latest Summary Data').

Paediatric scheme

Paediatric HIV surveillance began in 1986, and is run mainly through the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (BPSU, 2008; Nicoll *et al.*, 2000). Children with HIV infection and infants born to HIV-infected women are reported by paediatricians through the BPSU's orange card scheme (Appendix 2, page 374), an active monthly reporting system for rare conditions of childhood. Notified cases are reported to the NSHPC, and paediatricians are asked to complete a notification form (Appendix 2, page 375). Some paediatric units responsible for large numbers of HIV-exposed children report directly to the NSHPC. Following the initial report, additional information is requested to ascertain infection status (Appendix 2, page 379), and infected children are followed up annually, mainly through the Collaborative HIV Paediatric Study

(CHIPS), a collaboration between the NSHPC, the Medical Research Council (MRC) Clinical Trials Unit, and the paediatric centres looking after the children. Laboratory reports of HIV in children under the age of 16 are also provided by the Health Protection Agency (HPA) in England and Wales and by Health Protection Scotland (HPS). All incoming reports, both from paediatric respondents and from the HPA and HPS, are checked against previously reported children using dates of birth and other identifiers to avoid duplicates.

Data collection

NSHPC data collection forms are regularly updated in order to include new questions and refine old questions (Table 2.2). Each version of the form is dated, and this is recorded on the database for each reported case.

Information collected through the obstetric scheme includes maternal demographic details, mode of acquisition of HIV, time and place of HIV diagnosis, details of ART, recent laboratory investigations, and expected date of delivery. Ethnic origin is reported as white, black African, black Caribbean, Asian, Oriental, black other, mixed and other. HIV exposure categories include “from high prevalence area”, injecting drug use and HIV positive partner, with the option of specifying other exposures, such as receipt of transplant or blood product, occupational exposure, or sex work. Details of individual antiretroviral drugs taken in pregnancy are collected along with date (or gestation week) of initiation. Information on maternal clinical status is collected at the time of notification and at delivery. Maternal CD4 cell count has been collected since 1990, and HIV RNA plasma viral load since 1997; laboratory protocols and viral load assay types varied between hospitals and over time, but details are not routinely requested. Data collected at the time of delivery include date and mode of delivery, pregnancy complications, birth weight,

gestational age (recorded in completed weeks), sex of the infant and congenital abnormalities (identified by the time of notification, usually in the first few weeks of life). Information on maternal co-infections in pregnancy (including hepatitis C virus, hepatitis B virus and syphilis) has only been collected since July 2008, although some information on perinatal infections was available previously.

Mode of delivery was collected from 1995 onwards (Table 2.2), with the following categories: vaginal, elective caesarean section or emergency caesarean section, as reported by the respondent. In 2002 the question was modified to distinguish between planned and unplanned vaginal delivery. Questions about pregnancy complications and rupture of membranes were added to the data collection forms in 2004 and 2005, respectively (Table 2.2). Information on duration of ruptured membranes was added in 2007 and was therefore not available for analyses presented in this thesis.

Paediatric forms are designed for both HIV-infected children and infants born to infected women; information sought includes mode of transmission or exposure, how the child was identified as infected or at risk of infection, maternal and paternal demographic characteristics, exposure to ART in fetal life and neonatally, perinatal details, laboratory investigations, clinical details and vital status. Although the paediatric and obstetric forms overlap in terms of the data collected, some information was only collected through one scheme (Table 2.3).

Table 2.2 Changes to NSHPC data collection forms

Variables	Date added
Maternal co-infections	**Jul 2008**
Planned mode of delivery (vaginal or elective caesarean section)	**May 2007**
Duration of ruptured membranes	**May 2007**
Reason for maternal treatment (prevention of mother-to-child transmission or also maternal health)	**Dec 2005**
Ruptured membranes (yes/no)	**Dec 2005**
Pregnancy complications (e.g. pre-eclampsia)	**Jun 2004**
Birth weight (added to obstetric form)	**Jun 2004**
Whether vaginal delivery was planned or unplanned	**Mar 2002**
HIV RNA plasma viral load	**Sep 1997**
Mode of delivery	**Jan 1995**

N.B. CD4 cell count was requested throughout, but up to 1997 was reported for less than 50% of pregnancies.

Table 2.3 Variables collected only through one of the NSHPC schemes

Reported through:	Variables
Obstetric scheme only	Maternal clinical status (HIV-related symptoms or AIDS) ART at conception Date of initiation of ART HIV RNA viral load CD4 cell count Pregnancy complications Rupture of membranes / duration of rupture of membranes Whether vaginal delivery was planned or unplanned
Paediatric scheme only	Infection status Birth weight (up to January 2004; subsequently through both)

Data management

NSHPC data are managed in an Access 2003 database (Microsoft Corporation, Redmond, Washington, USA). All incoming reports are checked against previous reports, using dates of birth, to identify potential duplicates and match related cases:

- Initial pregnancy notifications are checked to ensure they are not duplicate reports, and are linked with previous pregnancies.
- Live births reported through the obstetric scheme are linked with paediatric cases.
- Paediatric notifications are checked to ensure they are not duplicate reports, and are linked with pregnancy notifications and outcomes, and with siblings.

Data quality is maintained through regular checks and data cleaning at different stages:

- At the data entry phase, inconsistencies that are detected are checked with respondents (e.g. non-chronological dates, mismatches between data collected on obstetric and paediatric forms).
- A series of Access queries (currently ~45), which detect inconsistencies and extreme values, are run on a quarterly basis; data entry errors are then corrected, and remaining inconsistencies are clarified with respondents.
- Additional checks are carried out in Stata (Stata Corporation, College Station, Texas, USA) before each analysis, and new check queries are added periodically as a result.

Datasets for analyses were extracted using Access queries, and obstetric and paediatric data were merged into a single dataset using R versions 2.1.2 to 2.8.0 (R Development Core Team, 2006).

Categories and definitions

Variable definitions and groupings used across different analyses are described here. Details of categorisation relevant to specific analyses are shown in the corresponding chapters.

Maternal characteristics

Ethnic origin was grouped into three categories: white, black African and other. For most analyses, likely route of HIV acquisition was categorised as 'injecting drug use' or 'non-injecting drug use'; the latter included all other routes, as well as those cases with no specified risk factors for HIV acquisition. Parity referred to the number of previous births, nulliparous meaning none and parous meaning one or more. Up to 2001, parity referred only to previous live births, whereas from 2002 onwards, it included previous stillbirths.

Maternal clinical and immunological characteristics

Maternal clinical status: Women were classified as symptomatic if AIDS or HIV-related symptoms were reported either at the time of first report or at delivery, and otherwise as asymptomatic (Centers for Disease Control and Prevention, 1992); in some analyses, clinical status at delivery was used.

CD4 cell counts: Only CD4 cell counts measured in pregnancy were considered; those measured just after delivery were excluded, since changes in lymphocyte levels associated with haemodilution may occur (Tuomala *et al.*, 1997). If multiple test results were reported, the one closest to delivery was selected. For some analyses, CD4 count was grouped according to commonly used categories: <200, 200-349, 350-499 and ≥500 cells/μl.

HIV RNA viral load: For most analyses, viral loads measured in pregnancy and up to seven days postpartum were considered, and the one closest to delivery was used. The only exception was the analysis in Chapter 5 (Section 5.2) on ART and prematurity in the NSHPC, in which viral loads measured at least one week after initiation of ART and up to 14 days postpartum were considered; the closest one to delivery was selected. Viral loads carried out just after delivery were considered because test results 'closest to delivery' were requested on the pregnancy outcome form, and in a small proportion of cases, the only test reported was carried out after delivery. When viral load was used as a continuous variable, it was $\log_{10}$ transformed (due to its non-normal distribution), and mid-points were used for values below the assay detection limits: for example, '<50 copies/ml' was coded as 25 copies/ml, and '<400 copies/ml' as 200 copies/ml (Gray, Cortina-Borja, & Newell, 2004). For some analyses, viral load was classified as <50 copies/ml (undetectable), 50-999 copies/ml, 1000-9999 copies/ml and ≥10,000 copies/ml, in order to distinguish between 'undetectable' and 'low but detectable' viral load, as well as to enable rates of adverse outcomes to be shown at different viral load levels. The category '50-999 copies/ml' included a small number of tests reported as '<200 copies/ml' or '<400 copies/ml', which are described in individual analyses.

Antiretroviral therapy

Exposure to ART in pregnancy was categorised according to the total number of drugs received: none, monotherapy (one drug), dual therapy (two drugs) or highly active antiretroviral therapy (HAART) (three or more drugs from any class). To explore the effect of different classes of drugs, regimens were categorised according to whether non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) were included, resulting in the following four categories: nucleoside reverse transcriptase inhibitors (NRTIs) only, NNRTI-containing regimens, PI-

containing regimens, and NNRTI- and PI-containing regimens. Date or gestation week of initiation of ART was collected only through the obstetric scheme; in most cases, dates were provided, but where completed week of gestation was provided, this was recoded as the middle of that week (e.g. 26 completed weeks was recoded as 26.5 weeks). Timing of ART exposure was classified as early if a woman started therapy prior to conception or in the first trimester (up to and including 12 completed weeks of gestation), and late if started after 12 weeks.

Pregnancy outcome and delivery

Spontaneous fetal death before 24 weeks gestation was defined as a miscarriage, and at 24 or more weeks gestation as a stillbirth (Royal College of Obstetricians and Gynaecologists, 2005). Perinatal death was defined as stillbirths and deaths in neonates occurring less than seven completed days from the time of birth (Confidential Enquiry into Maternal and Child Health, 2006).

Gestational age was categorised as ≤32, 32-34, 35-36 and ≥37 weeks gestation; premature, or preterm, delivery was defined as delivery before 37 completed weeks gestation, and severe prematurity as delivery before 32 weeks gestation (Goldenberg *et al.*, 2008). In addition, delivery before 35 weeks gestation was chosen as an additional cut-off to exclude 'near-term' infants born at 35 or 36 weeks (Wang *et al.*, 2004). Low birth weight was defined as <2500 g, and very low birth weight as <1500 g (UNICEF/WHO, 2004).

Elective caesarean section referred to scheduled caesarean section deliveries carried out before onset of labour or rupture of membranes; most were carried out for prevention of mother-to-child transmission, but additional reasons for elective caesarean section included twin pregnancy, breech presentation, previous caesarean section, maternal request and macrosomia (large baby) (Royal College of

Obstetricians and Gynaecologists, 2004). Emergency caesarean section deliveries included those carried out after rupture of membranes and/or onset of labour, as well as those carried out for other obstetric indications (e.g. pre-eclampsia, fetal distress, etc); if a delivery was reported as elective caesarean section, but rupture of membranes or labour was recorded, it was re-classified as an emergency.

Congenital abnormalities

Congenital abnormalities were classified using the World Health Organization's International Classification of Diseases, 10th revision (World Health Organization, 1992). For infants with multiple abnormalities reported, only the main one was included in the analysis. Detailed information on whether abnormalities were major or minor was not routinely collected; however, in order to estimate the prevalence of major abnormalities, the following were classified as minor: polydactyly, abnormalities of the feet, malformed ear, minor mouth abnormalities, macroglossia, undescended testes, accessory nipple, spinal hairy patch, strawberry naevus, birthmark, skin tag, and subclinical sub-ependymal cysts (see Table 4.13, page 141). These classifications were mostly consistent with those used by EUROCAT, the European congenital anomaly surveillance system (EUROCAT, 2005). Additional information is required for classification of talipes and polydactyly. As this was not available in the NSHPC, talipes was classified as major, and polydactyly as minor in these analyses.

Infection status

Non-breastfed infants were classified as 'presumed uninfected' if a negative HIV DNA or RNA PCR test after one month of age was reported and 'confirmed uninfected' following a subsequent negative PCR after three months of age or a negative HIV antibody test after 18 months of age. Infants were classified as

'presumed infected' if a positive PCR test was reported, and 'confirmed infected' if two positive PCR tests were reported, or if a positive antibody test after 18 months of age was reported. Surveillance definitions of infection status, which are sent to paediatric respondents, are shown in Appendix 2 (pages 377 and 380). Because preliminary results rarely conflict with later ones, and infants were mostly not breastfed, 'presumed' and 'confirmed' results were grouped in the analyses. PCR test results at birth were not routinely available, and in most cases it was not possible to establish timing of infant infection (whether *in utero* or at delivery). However, for infants with a PCR test result reported within the first 72 hours of life, those with a positive test were considered to have been infected *in utero* (Bryson *et al.*, 1992).

Ethics Approval

The NSHPC is approved by the London Multi-centre Research Ethics Committee (MREC) (Reference: MREC/04/2/009, approved on 28 January 2004). In addition, as the surveillance is carried out in collaboration with the BPSU and the HPA, without individual patient consent, it is also covered by Section 60 of the Patient Information Advisory Group, under the Health and Social Care Act 2001.

The European Collaborative Study

The European Collaborative Study (ECS) is a prospective multi-centre cohort study of HIV-infected pregnant women, coordinated at the UCL Institute of Child Health in London (European Collaborative Study, 2007). The study was established in 1986 (European Collaborative Study, 1988), and in 2006 included centres in 10 European countries (Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden, the Ukraine, and the UK). Women known to be HIV-infected when they become pregnant, and those diagnosed in pregnancy are invited to enrol in the study,

and informed consent is obtained. Local ethics approval is granted for each site. Information is collected at enrolment and during pregnancy, and children born to enrolled women are followed up according to standard protocols. Information collected includes maternal socio-demographic characteristics, likely route of HIV acquisition, obstetric history, use of ART, CD4 cell count, HIV RNA plasma viral load, and delivery and neonatal details (Appendix 3).

Categories and definitions

Ethnic origin in the ECS was categorised as white, black African or other. ART was categorised as none, monotherapy, dual therapy or HAART (three or more drugs), and HAART was categorised according to whether PIs or NNRTIs were included. History of injecting drug use was recorded. Gestational age was recorded in completed weeks. Mode of delivery was categorised as vaginal, elective caesarean section (before onset of labour or rupture of membranes) or emergency caesarean section. Maternal CD4 cell count and viral load tests were carried out locally, and those closest to delivery were selected. Children were classified as infected if a positive virological or serological marker of infection was detected, or if antibody persisted after 18 months of age; and as uninfected if they were antibody-negative and no virus or antigen had ever been detected.

The Pediatric Spectrum of HIV Disease project

The Pediatric Spectrum of HIV Disease (PSD) project was a prospective epidemiological review of newborn and paediatric medical records of HIV-exposed and HIV-infected live born infants in the United States, based at eight geographic sites from 1989 to 1997, and six sites from 1997 to 2004 (Figure 2.2). The study was run through the Centers for Disease Control and Prevention (CDC) in Atlanta,

Georgia. It was based in several hospitals in New York City and the District of Columbia, but had wider coverage in California, Massachusetts and North Carolina, and was considered population-based in those areas. In Texas and Puerto Rico, the study initially included single hospitals, but in 1997 was extended to cover others.

The PSD was approved by the CDC Institutional Review Board, and was also reviewed and approved locally. Hospitals were visited by study personnel on a regular basis, and children were identified by contact with key practitioners, and by review of HIV laboratory logs and medical records. After initial data collection, records on each enrolled child were reviewed every six months. Data were collected mainly from paediatric medical notes, but maternal charts could also be reviewed if included in the paediatric records. Data were collected on standard forms (Appendix 4) and entered into a CDC database at each site. Study personnel had periodic training on medical record abstraction and on any changes in the data collection methods (e.g. when HIV case definitions changed), and detailed form completion instructions were available.

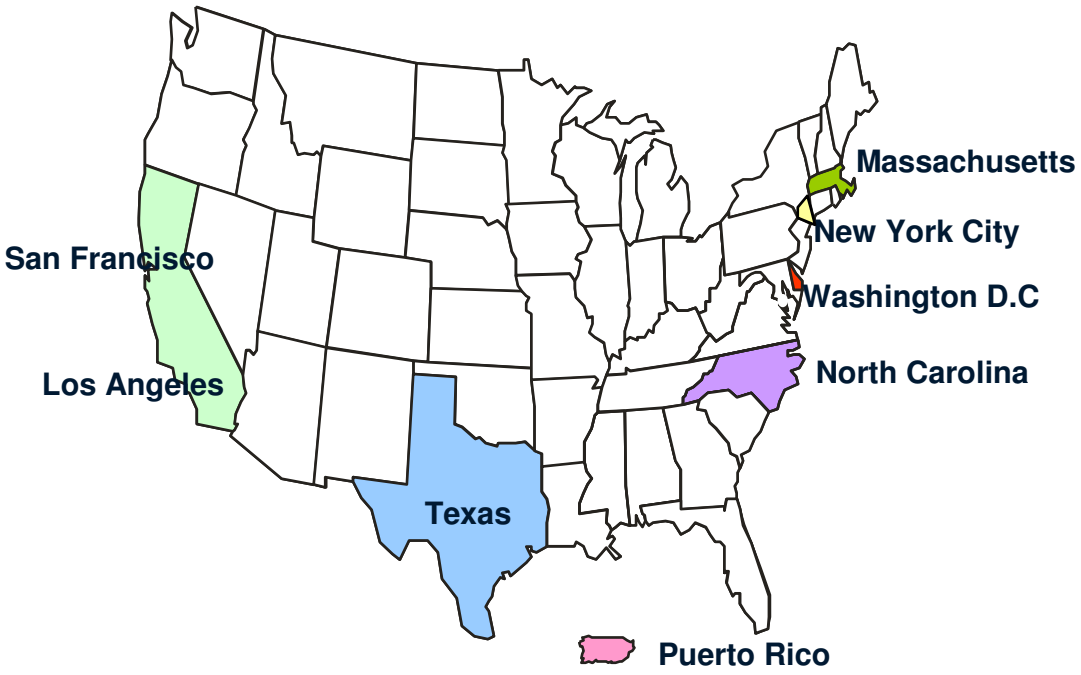
Data collected included maternal race/ethnicity and country of birth, presence of HIV symptoms at delivery, history of injecting drug use, antenatal ART, mode of delivery, birth weight and gestational age. Because the PSD was based on paediatric records, maternal age, HIV viral load and CD4 cell count were not available.

Categories and definitions

Ethnic origin was categorised as white (non-Hispanic), black (non-Hispanic), Hispanic, or other. Exposure to antenatal ART was categorised according to the number of drugs received: none, monotherapy, dual therapy or HAART; HAART was categorised according to whether or not a PI was included. Gestational age was

recorded in completed weeks. Mode of delivery was categorised as vaginal or caesarean section; information on whether caesarean sections were elective or emergency was only collected from 2003. Maternal clinical status was classified as symptomatic if AIDS or HIV-related symptoms were reported at delivery (Centers for Disease Control and Prevention, 1992). Infection status of the child was based on CDC classifications (Centers for Disease Control and Prevention, 1999).

Figure 2.2 Pediatric Spectrum of HIV Disease (PSD) project sites



N.B. San Francisco (Stanford) and North Carolina were sites until 1997 only.

2.3 Comparative analysis of antiretroviral therapy and prematurity in three studies

Dataset

Singleton live born infants whose mothers were diagnosed with HIV before delivery were selected from the PSD, the ECS and the NSHPC. As there was some overlap between women enrolled in UK ECS centres and those reported through the NSHPC, these cases were excluded from the NSHPC dataset (*n*=200). Because information on stillbirths was not routinely collected in the PSD and ECS, stillbirths were also excluded from the NSHPC dataset. Infants with missing information on maternal ART were excluded from the PSD and ECS datasets, as were those with missing information on maternal ethnicity in the PSD. ECS centres in the Ukraine were excluded (*n*~2600 births), as they only joined the study in 2000 and included few women on HAART (~5%). In the ECS and NSHPC, it was possible to identify mothers who had more than one child during the study period, but information on repeat pregnancies was not available in the PSD. Data from the PSD, ECS and NSHPC were combined into one dataset in Stata version 10.0 (Stata Corporation, College Station, Texas, USA), in order to explore the association between ART and prematurity in the three studies.

Statistical methods

Heterogeneity between studies in the association between ART and prematurity was assessed using a χ^2 test of homogeneity of odds ratios (Kirkwood & Sterne, 2003). Inclusion of covariates in logistic regression models was based on likelihood ratio tests. To allow for the effect of study site and mother (i.e. repeat pregnancies in the

same woman), generalized linear mixed effects were used (commands '`xtlogit`' and '`xtmelogit`' in Stata, for single and multilevel effects, respectively) (Rabe-Hesketh, Skrondal, & Pickles, 2002).

2.4 Statistical analysis

Data analysis was carried out using Stata versions 8.0-10.0 (Stata Corporation, College Station, Texas, USA), or in R versions 2.1.2 to 2.8.0. (R Development Core Team, 2006).

Categorical variables were compared using χ^2 tests or Fisher's exact tests if numbers in individual cells were small. Means were compared using *t*-tests, and medians using Kruskal-Wallis tests. Trends in medians were assessed using Cuzick's non-parametric test for trend across ordered groups (function '`nptrend`' in Stata) (Cuzick, 1985). Univariable logistic regression models were fitted to obtain odds ratios (ORs), and multivariable models to adjust for potential confounders, and to obtain adjusted odds ratios (AORs) and 95% confidence intervals (CI). Ordinary logistic regression models were used to obtain *p*-values for trends in means or proportions. Likelihood ratio tests (LRTs) were used to compare nested logistic regression models. The LRT is a statistical test of the goodness-of-fit of one model compared with another. Interactions were explored using stratified Mantel-Haenszel ORs and tested using a χ^2 test of homogeneity. Evidence of interaction was further investigated in logistic regression models.

2.5 Risk-benefit analysis of antiretroviral therapy in pregnancy

In Chapter 6, results of a Monte Carlo simulation of the risks and benefits of ART are presented. Because the methodology diverges substantially from that used in other chapters, details are provided in the chapter itself.

2.6 List of analyses based on the NSHPC

The NSHPC is an ongoing surveillance study, and datasets are compiled every three months. Analyses were carried out on the dataset that was most up-to-date at the time of analysis, as shown in Table 2.4.

Table 2.4 List of NSHPC analyses

Analysis	Chapter	Time period	Cut-off	Number included
Pregnancies in HIV-infected women	3	1990-2006	Jun 2007	8327 pregnancies
Mother-to-child transmission in the HAART era	3	2000-2006	Jun 2007	5930 singleton infants
ART and congenital abnormalities	4	1990-2007	Jun 2008	8576 infants
ART and stillbirth/neonatal death	4	1990-2007	Jun 2008	8430 births
ART and pre-eclampsia	4	2004-2007	Jun 2008	3852 pregnancies
ART and prematurity - NSHPC analysis	5	1990-2005	Jun 2006	5009 singleton infants
ART and prematurity - comparative analysis	5	1990-2006	Jun 2007	6665 singleton live born infants
Mother-to-child transmission, early monotherapy comparison	6	1990-2006	Jun 2007	4454 singleton infants (mono & HAART only)

Chapter 3 Pregnancies in HIV-infected women in the UK and Ireland

Substantial changes in the epidemiology of HIV in Western Europe have occurred over the last two decades (Hamers & Downs, 2004). At the same time, advances in the prevention of mother-to-child transmission (MTCT) have led to a decline in transmission rates to less than 2% (European Collaborative Study, 2001; European Collaborative Study, 2005d). These developments are reflected in the profile of HIV-infected pregnant women and their children in the UK and Ireland.

In the first part of this chapter, trends in demographic characteristics, uptake of interventions, pregnancy outcome and MTCT in HIV-infected women in the UK and Ireland are described, in the context of changing guidelines for the management of HIV in pregnancy (BHIVA, 2001; BHIVA, 2005a; BHIVA/CHIVA, 2008). In the second part of the chapter, factors associated with MTCT are explored in infants born between 2000 and 2006, when effective antiretroviral therapy and universal antenatal HIV screening were widely available. Papers relating to these findings were published in 2008 and are shown in Appendix 2, pages 339 (Townsend *et al.*, 2008b) and 348 (Townsend *et al.*, 2008a).

3.1 Methods specific to this chapter

All reported pregnancies in women diagnosed with HIV before delivery, delivering between 1990 and 2006, and reported to the National Study of HIV in Pregnancy and Childhood (NSHPC) by June 2007 were included. For calculation of overall MTCT

rates between 1990 and 2006, all live births were included, although second- and third-born twins and triplets were omitted to avoid duplication of information (European Collaborative Study, 1999; Warszawski *et al.*, 2008). To explore specific risk factors for MTCT in 2000-2006, analyses were restricted to singleton live births, since complications are more common in multiple pregnancies (Rao, Sairam, & Shehata, 2004) and may alter the risk of transmission. Births were described by year of delivery and other pregnancy outcomes by year of 'expected date of delivery'. To explore trends over time, years were grouped into five time periods according to availability of interventions (Table 3.1). Clinical status referred to HIV-related symptoms or AIDS occurring at any time in pregnancy (i.e. reported at initial notification or at delivery).

Analyses were based on pregnancies, and some women were included more than once (see page 73). In the MTCT analysis covering 2000-2006, no woman had more than one infected child born in those years.

Table 3.1 Time periods and availability of interventions relating to prevention of mother-to-child transmission

Time period	Intervention	Reference
1990-1993	Avoidance of breastfeeding	(Dunn *et al.*, 1992; Ziegler *et al.*, 1985)
1994-1996	Zidovudine monotherapy	(Connor *et al.*, 1994)
1997-1999	HAART; elective caesarean section	(Collier *et al.*, 1996; European Collaborative Study, 1996b)
2000-2003 2004-2006	Routine antenatal HIV screening	(NHS Executive, 1999)

HAART, highly active antiretroviral therapy.
N.B. The period from 2000 to 2006 was split into two, due to the large number of pregnancies reported, and because of changes in uptake of HIV testing and interventions over this period.

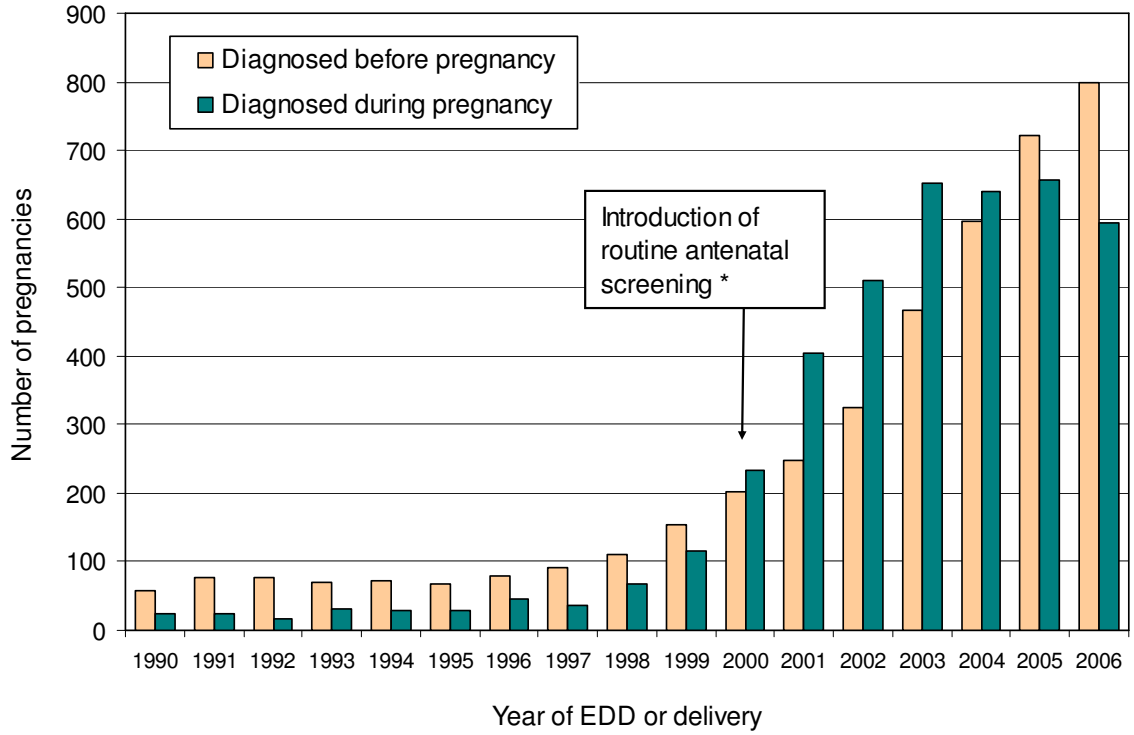
Reporting rates by geographical area were obtained by dividing the annual number of pregnancies in HIV-infected women reported in each country and English strategic health authority by the number of resident women aged 15 to 49 years, derived from mid-year 2000 census data for the UK (Office for National Statistics, 2000), and 2002 census data for Ireland (Central Statistics Office Ireland, 2002). Maps were drawn using R version 2.4.1 (R Development Core Team, 2006). *P*-values in Tables 3.2 and 3.3 were adjusted for multiple comparisons using a Bonferroni correction (Miller, 1981).

Infection status was defined in Chapter 2 (page 61). The effect of excluding infants with missing information on infection status was explored in a sensitivity analysis (pages 106-107). The probability of being infected was imputed, based on variables that were significantly associated with transmission in the analysis, using the '`impute`' function in Stata. Relevant variables included: maternal antiretroviral therapy (ART) in pregnancy (none, monotherapy, dual therapy or highly active antiretroviral therapy [HAART]), mode of delivery (planned, unplanned or unspecified vaginal delivery, or elective or emergency caesarean section), gestational age (≤32, 32-34, 35-36 and ≥37 weeks), infant sex, and $\log_{10}$ HIV RNA viral load.

3.2 Pregnancies in HIV-infected women

Between 1990 and 2006, 8327 pregnancies in 6788 HIV-infected women were reported; 5540 women had one pregnancy reported during the study period, 1010 two, and 238 three or more. The annual number of reported pregnancies increased 17-fold, from 82 in 1990 to 1394 in 2006, the steepest rise occurring between 1999 and 2003 (Figure 3.1). There were 116 multiple births: in one twin pair one infant was stillborn, and there were two twin stillbirths (i.e. five stillborn infants altogether). Pregnancy outcomes included 6979 live births, 77 stillbirths, 329 miscarriages and 519 terminations (Table 3.2). There were 423 pregnancies with other or unknown outcomes, which included two maternal deaths (one suicide and one death from HIV encephalopathy, both of which occurred in the mid 1990s) and 23 ectopic pregnancies (all ending before 13 weeks gestation); 110 women were known to have left the British Isles before delivery and another 109 were otherwise lost to follow-up. At the time of analysis (June 2007), information on pregnancy outcome was still pending on 179 pregnancies due to end in 2004-2006 (Table 3.2). The proportion of pregnancies in nulliparous women increased significantly from 12% in 1990-1993 to 35% in 2004-2006.

Figure 3.1 Number of pregnancy reports by year of delivery, according to whether maternal diagnosis occurred before or during pregnancy.



EDD, expected date of delivery.
* (NHS Executive, 1999; Townsend, Cliffe, & Tookey, 2006).

Table 3.2 Pregnancy characteristics by time period

Characteristic (8327 pregnancies)	1990-1993 (*n*=376)		1994-1996 (*n*=325)		1997-1999 (*n*=576)		2000-03 (*n*=3041)		2004-06 (*n*=4009)		Total (*n*=8327)	*p*-value (trend)
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	
Pregnancy outcome (n=8327)												
Live birth	235	**62.5**	260	**80.0**	456	**79.2**	2623	**86.3**	3405	**84.9**	6979	<0.005
Stillbirth	1	**0.3**	2	**0.6**	7	**1.2**	24	**0.8**	43	**1.1**	77	>0.50
Miscarriage	15	**4.0**	5	**1.5**	32	**5.6**	119	**3.9**	158	**3.9**	329	>0.50
Termination of pregnancy	111	**29.5**	48	**14.8**	70	**12.2**	155	**5.1**	135	**3.4**	519	<0.005
Other / outcome not known *	14	**3.7**	10	**3.1**	11	**1.9**	120	**3.9**	268	**6.7**	423	NA
Timing of diagnosis (n=8327)												
Before this pregnancy	279	**74.2**	220	**67.7**	357	**62.0**	1242	**40.8**	2117	**52.8**	4215	<0.002
During this pregnancy	97	**25.8**	105	**32.3**	219	**38.0**	1799	**59.2**	1892	**47.2**	4112	<0.002
Parity (n=6569)												
Nulliparous (no previous births)	5	**11.9**	48	**19.4**	105	**20.4**	881	**35.1**	1136	**34.9**	2175	<0.002
Parous (≥1 previous birth)	37	**88.1**	200	**80.6**	409	**79.6**	1629	**64.9**	2119	**65.1**	4394	<0.002
*Region of pregnancy report (n=8321**)*												
London	191	**50.8**	210	**65.0**	437	**76.0**	1728	**56.9**	1803	**45.0**	4369	NA
England outside London	65	**17.3**	51	**15.8**	72	**12.5**	823	**27.1**	1711	**42.7**	2722	NA
Scotland, Wales, Northern Ireland	91	**24.2**	49	**15.2**	30	**5.2**	90	**3.0**	166	**4.1**	426	NA
Ireland	29	**7.7**	13	**4.0**	36	**6.3**	397	**13.1**	329	**8.2**	804	NA

* Includes 179 pregnancies due to end in 2004-2006 for which outcome was still pending at the time of analysis (June 2007); trend test not appropriate for this group.
** Excludes six infants born in the Channel Islands.
NA, not applicable. *P*-values are for trends over time, comparing each category against all others combined, and were obtained using logistic regression and adjusted for multiple comparisons using a Bonferroni correction.

Demographic characteristics of HIV-infected women

There were marked changes over time in the demographic profile of HIV-infected pregnant women (Table 3.3). The proportion of all women reported to have probably acquired HIV through injecting drug use or from a drug-using partner declined 10-fold, from around half in 1990-1993 to less than 5% in 2004-2006 (Table 3.3). Meanwhile the proportion of women born in sub-Saharan Africa increased from under half in 1990-1993 to almost 80% in 2004-2006, with a corresponding change in maternal ethnic origin (Table 3.3). There was also a statistically significant rise in the proportion of women born in Asia, from 0% (0/214) in 1990-1993 to 2.2% (87/3912) in 2004-2006 (trend: p=0.003). As a proportion of all women with either country of birth or ethnicity reported, those born in the Caribbean or of black Caribbean ethnicity increased from 1.4% (4/293) in 1990-1993 to 3.7% (147/3989) in 2004-2006 (trend: p=0.051). Among women who were born abroad, information on date of arrival in the British Isles was only available for 55.6% (3735/6714); among these, median time between arrival and delivery was 3.3 years (interquartile range [IQR]: 1.4-6.1 years). Seven women were known to have acquired infection vertically from their own mothers; all delivered (n=5) or terminated their pregnancy (n=2) between 2004 and 2006, and were aged between 15 and 20 years at the time of delivery or expected date of delivery; four were born in the British Isles.

Median maternal age at delivery increased over time, from 27.2 years (IQR: 24.4-30.1 years) in 1990-1993 to 30.2 years (IQR: 26.4-34.0 years) in 2004-2006 (trend for grouped years, p<0.001). Mean maternal age in the UK as a whole has increased steadily over time, rising from 26.2 years in 1983 to 28.6 years in 2001 among UK-born women, and 27.3 years to 31.7 years in East African women (Collingwood,

2004). There was no evidence of a significant increase over time in the proportion of teenage pregnancies (those in women under the age of 20), which was 2.8% (10/358) in 1990-1993, 3.9% (22/571) in 1997-1999, and 3.4% (134/3982) in 2004-2006 (trend: p=0.276). In the general population in the UK, the proportion of babies born to women under 18 fluctuated between two and three percent between 1976 and 2000 (Maher & Macfarlane, 2004).

Up to 1999, the majority of pregnancies were in women who already knew their HIV status before they became pregnant (67.0%, 856/1277) (Figure 3.1, page 74, and Table 3.2). As universal antenatal HIV screening was introduced throughout the British Isles, the proportion of women diagnosed during pregnancy rose to 60.1% (1566/2606) between 2001 and 2003, and then declined subsequently (Figure 3.1). The corresponding increase in women diagnosed before pregnancy was probably partly due to women diagnosed antenatally in the early years of routine screening becoming pregnant again in later years. Indeed, among women who knew their HIV status at conception (and with information on where their diagnosis was made), the proportion diagnosed in a previous pregnancy doubled from 18.0% (24/133) in 2000 to 36.1% (181/502) in 2006 (trend: p<0.001). Overall, 2.9% (120/4112) of antenatal diagnoses were made in the last two weeks of pregnancy, by which time the opportunity to reduce the risk of MTCT with maternal ART was substantially reduced.

The prevalence of AIDS or HIV-related symptoms in pregnancy remained stable at over 20% between 1990 and 1999 (trend, p=0.850), then declined from 18% (46/252) in 1999 to 12% (47/390) in 2000 (p=0.040), remaining at a stable 11% thereafter (trend from 2000 to 2006: p=0.846).

Table 3.3 Maternal characteristics by time period

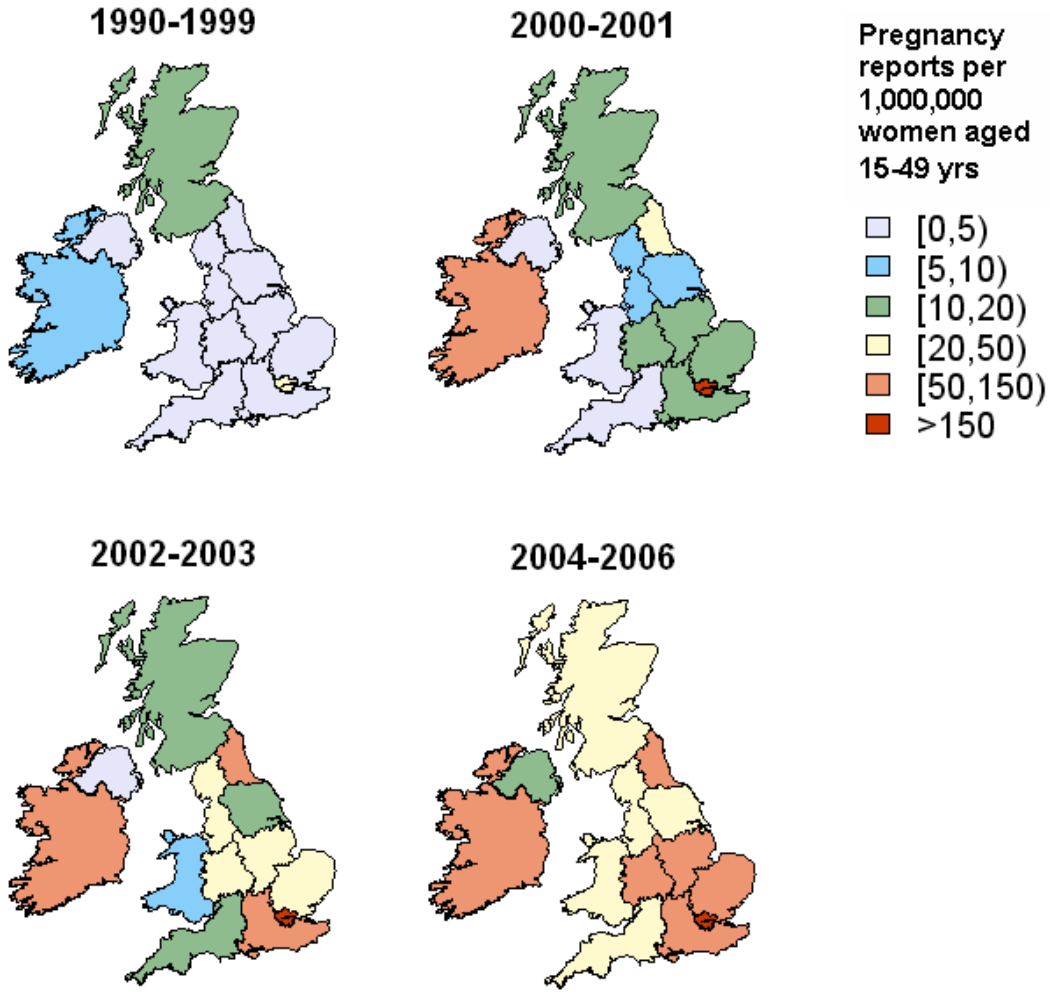
	1990-1993 (*n*=376)		1994-1996 (*n*=325)		1997-1999 (*n*=576)		2000-03 (*n*=3041)		2004-06 (*n*=4009)		Total (*n*=8327)	*p*-value (trend)
Characteristic (8327 pregnancies)	*n*	**%**	*n*	**%**	*n*	**%**	*n*	**%**	*n*	**%**	*n*	
Exposure category (n=8327)												
Injecting drug use-associated *	185	**49.2**	94	**28.9**	91	**15.8**	168	**5.5**	125	**3.1**	663	<0.003
Other **	191	**50.8**	231	**71.1**	485	**84.2**	2873	**94.5**	3884	**96.9**	7664	<0.003
Region of birth (n=8009)												
UK / Ireland	105	**49.1**	101	**32.8**	143	**25.0**	450	**15.0**	496	**12.7**	1295	<0.004
Europe (excluding UK / Ireland)	9	**4.2**	13	**4.2**	21	**3.7**	69	**2.3**	121	**3.1**	233	>0.50
Sub-Saharan Africa	93	**43.5**	179	**58.1**	381	**66.6**	2309	**76.9**	3076	**78.6**	6038	<0.004
Elsewhere	7	**3.3**	15	**4.9**	27	**4.7**	175	**5.8**	219	**5.6**	443	0.016
Ethnic origin (n=8157)												
White	167	**57.6**	127	**39.3**	150	**26.1**	427	**14.1**	492	**12.5**	1363	<0.003
Black African	115	**39.7**	183	**56.7**	388	**67.5**	2357	**78.0**	3140	**79.5**	6183	<0.003
Other	8	**2.8**	13	**4.0**	37	**6.4**	236	**7.8**	317	**8.0**	611	<0.003
Age at delivery (n=8244)												
14-24 years	107	**29.9**	63	**19.9**	101	**17.7**	557	**18.5**	704	**17.7**	1532	<0.003
25-34 years	235	**65.6**	234	**73.8**	379	**66.4**	1940	**64.3**	2463	**61.9**	5251	<0.003
≥35 years	16	**4.5**	20	**6.3**	91	**15.9**	519	**17.2**	815	**20.5**	1461	<0.003
Clinical status in pregnancy (n=7253)												
Asymptomatic	258	**78.2**	210	**74.7**	428	**80.6**	2413	**89.0**	3026	**89.0**	6335	<0.003
HIV-related symptoms or AIDS	72	**21.8**	71	**25.3**	103	**19.4**	299	**11.0**	373	**11.0**	918	<0.003

* Includes women whose partners acquired HIV through injecting drug use (*n*=195). ** Includes women with missing exposure information.
P-values are for trends over time, comparing each category against all others combined, and were obtained using logistic regression and adjusted for multiple comparisons using a Bonferroni correction.

Geographic patterns in pregnancy reporting

There were changes over time in the origin of pregnancy reports within the UK and Ireland. The proportion of pregnancies reported from London increased significantly from about 50% in 1990-1993 to 76% in 1997-1999 (trend: $p<0.001$) (Table 3.2, page 75). Subsequently, although the number of reports from London continued to rise until 2004, when they stabilised, the proportion reported from elsewhere in England increased significantly from 12.5% in 1997-1999 to 42.7% in 2004-2006 (trend: $p<0.001$) (Table 3.2). Figure 3.2 shows annual reporting rates (number of reports per million women aged 15-49 years) across the UK and Ireland in four time periods. By 2004-2006, rates in most areas of the UK were similar to those in London in 1990-1999. In Ireland, reporting rates stabilised following a substantial rise in the number of reports from only 13 in 1999 to almost 150 in 2003.

Figure 3.2 Pregnancy reporting rates in the UK and Ireland by time period and country/region



N.B. Reporting rates were obtained by dividing the annual number of reported pregnancies in HIV-infected women by the number of resident women aged 15 to 49 years, derived from 2000 census data for the UK (Office for National Statistics, 2000), and 2002 census data for Ireland (Central Statistics Office Ireland, 2002).

Terminations and miscarriages

The proportion of reported pregnancies ending in termination decreased 10-fold from around 30% in 1990-1993 to 3% in 2004-2006 (Table 3.2). Termination was 2.6 times more common in women diagnosed with HIV before pregnancy than in those diagnosed antenatally (OR=2.65, 95% CI: 2.18-3.23, $p<0.001$). However, similar declines occurred in both groups: termination rates fell from 34.7% in 1990-1993 to 4.1% in 2004-2006 among women diagnosed before pregnancy (trend: $p<0.001$), and from 20.2% to 2.7% among those diagnosed during pregnancy (trend: $p<0.001$). There was no association between HIV exposure category or maternal age and termination after adjusting for year and timing of diagnosis in multivariable logistic regression analysis ($p>0.50$ in both cases). Median gestational age at termination was 10 weeks (IQR: 9-13 weeks) for women diagnosed before pregnancy, and 15 weeks (IQR: 12-19 weeks) for those diagnosed during pregnancy ($p<0.001$). About 30% (101/335) of previously diagnosed women having terminations were taking ART at conception. Three terminations were carried out after 24 weeks: one at 25 weeks for major congenital heart defects, one at 30 weeks for anencephaly, and one at 29 weeks because of concerns about the woman's mental health.

Four percent (329/8327) of reported pregnancies resulted in a miscarriage; 80.9% (266/329) occurred before 20 weeks gestation, 10.3% (34/329) at 20-21 weeks and 8.8% (29/329) at 22-23 weeks. The overall rate of reported miscarriage remained constant over time (trend: $p=0.951$), as did the rate of late miscarriages ($\geq$ 20 weeks) (trend: $p=0.890$).

Live births and stillbirths

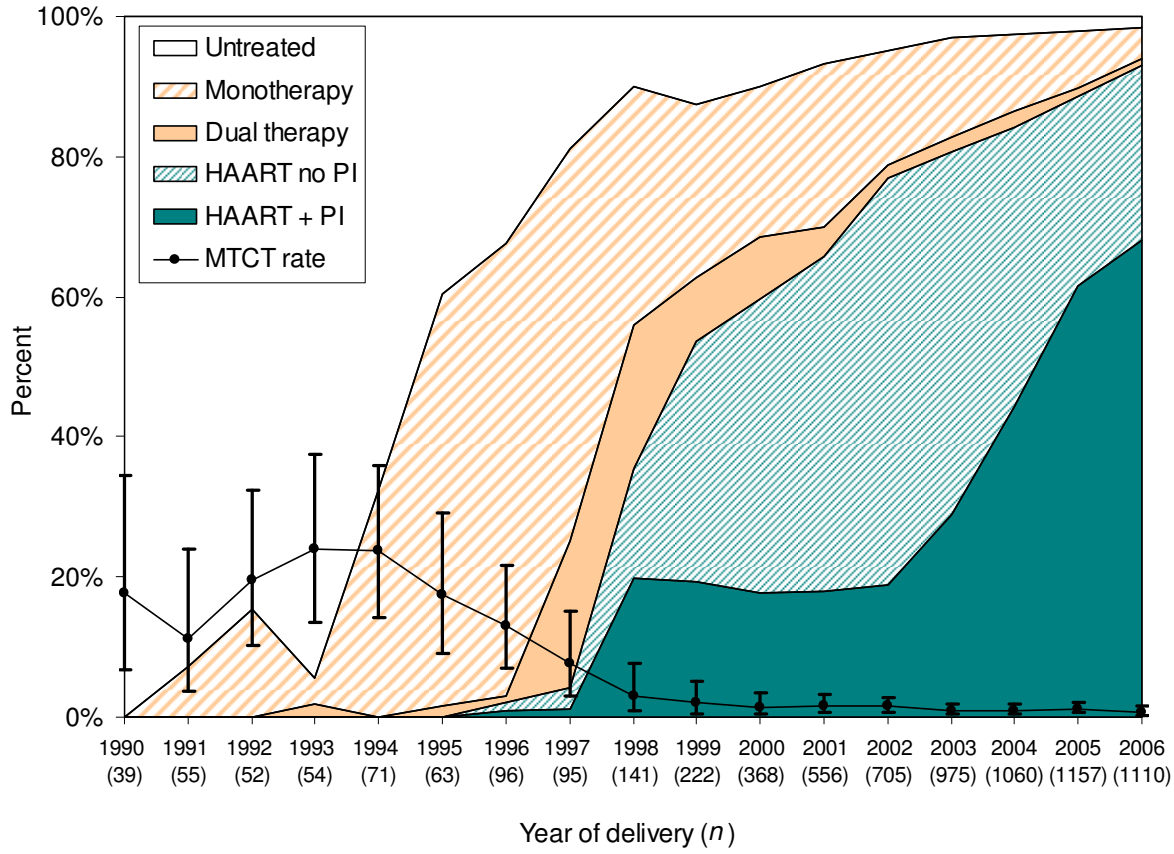
The following results refer to the 85% pregnancies (7056/8327) resulting in a live birth (*n*=6979) or stillbirth (*n*=77).

Antiretroviral therapy

Changes in the use of ART over time are shown in Figure 3.3. Following the introduction of zidovudine for the prevention of MTCT in 1994 (Connor *et al.*, 1994), uptake of ART (mostly monotherapy) increased rapidly. Although monotherapy has continued to be offered in some circumstances, as indicated in the British HIV Association (BHIVA) Guidelines (BHIVA, 2001; BHIVA, 2005a; BHIVA/CHIVA, 2008), it was overtaken by HAART in the late 1990s. By 2006, 98.4% (1092/1110) of diagnosed pregnant women received ART at some time in pregnancy, 94.5% (1032/1092) of whom received HAART and 4.4% (48/1092) monotherapy (Figure 3.3).

The type of HAART regimens changed over time, with an increase in the use of protease inhibitors (PIs) among HAART-treated women, which doubled from 36.1% (43/119) in 1999 to 73.2% (755/1032) in 2006 ($p<0.001$) (Figure 3.3). This pattern was probably associated with toxicity concerns relating to use of nevirapine (up until then the most commonly used non-nucleoside reverse transcriptase inhibitor [NNRTI]) among women with CD4 counts above 250 cells/µl (Lyons *et al.*, 2003). Evidence supporting this includes higher median CD4 counts in women on PIs in 2006 than those on other HAART regimens (420 cells/µl versus 330 cells/µl, $p<0.001$). Women on PIs were also more likely to have been diagnosed during, rather than before, pregnancy (48.1%, 363/755, versus 28.9%, 80/277, $p<0.001$).

Figure 3.3 Antiretroviral therapy and mother-to-child transmission rates (with 95% confidence intervals) by year of delivery



PI, protease inhibitor; MTCT, mother-to-child transmission.

Among pregnancies in previously diagnosed women, timing of initiation of ART (before or during pregnancy) was available for 87.3% (2942/3369); once combination therapy became available, the proportion on treatment at conception rose rapidly and then stabilised at around 45% (1188/2544) between 1999 and 2006 (trend: p=0.936). Information on reason for treatment was available only in 2006: among women who initiated HAART during pregnancy, 69.2% (258/373) did so only to prevent MTCT, with no difference according to whether maternal diagnosis was before (69.3%, 104/150) or during pregnancy (69.1%, 154/223, p=0.955).

CD4 counts and viral load

As the uptake of HAART increased, significant overall improvements in CD4 count and viral load occurred. CD4 count in pregnancy was reported for 75.9% (4901/6459) of births between 1998 and 2006, at a median of 29 days before delivery (IQR: 14-55 days). In later years, CD4 tests tended to be closer to delivery, at a median of 28 days (IQR: 13-53 days) before delivery in 2005-2006, compared with 37 days (IQR: 15.5-83.5 days) in 1998-1999 (trend for individual years: p<0.001). Median CD4 count increased significantly, from 315 cells/µl (IQR: 225-425 cells/µl) in 1998 to 395 cells/µl (IQR: 270-570 cells/µl) in 2006 (trend, p<0.001).

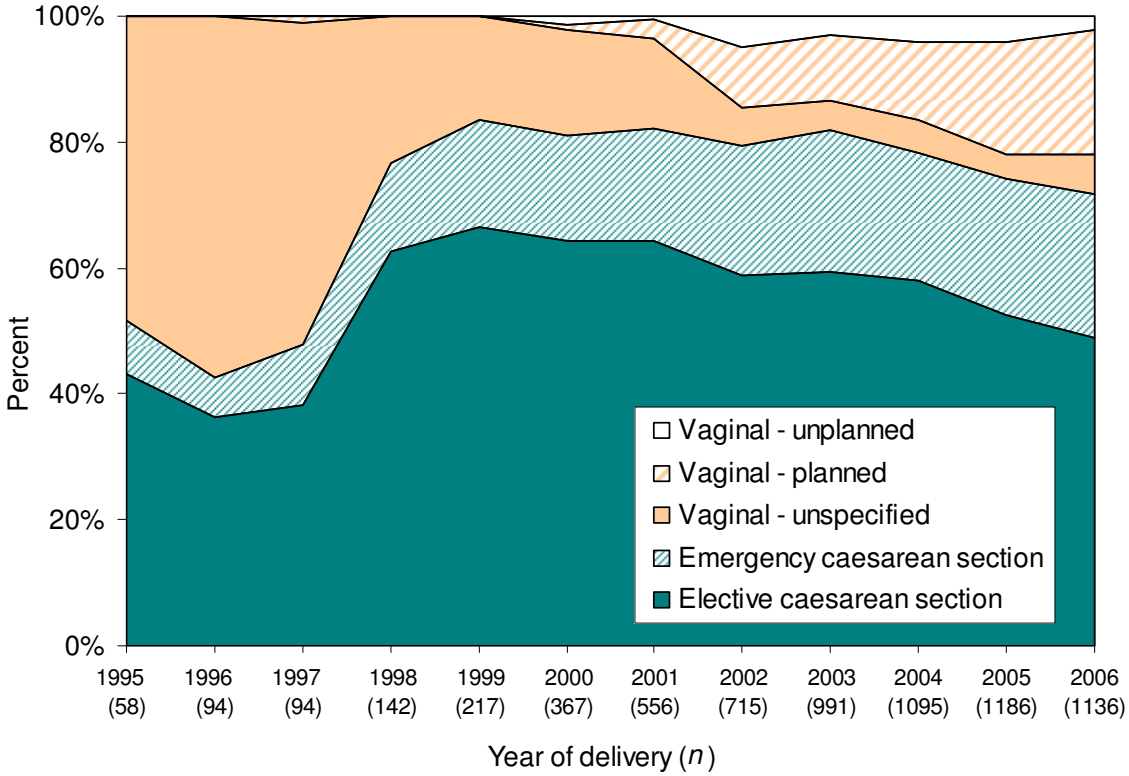
Viral load was reported for 78.8% (5092/6459) of births between 1998 and 2006, at a median of 24 days before delivery (IQR: 10-45 days). As with CD4 tests, there was a decline in median time between viral load tests and delivery from 27 days (IQR: 14-69 days) in 1998-1999 to 22 days (IQR: 10-42 days) in 2005-2006 (trend for individual years: p<0.001). A small proportion of viral load tests were reported as 'less than 200' (n=57) or 'less than 400' copies/ml (n=110), due to the detection limits of the assays used; these were recoded as 100 and 200 copies/ml, respectively. The proportion with viral load <50 copies/ml increased from 29.0% (27/93) in 1998

to 69.0% (609/882) in 2006 (trend: $p<0.001$). Median viral load decreased from 1992 copies/ml (IQR: <50-8400 copies/ml) in 1998 to <50 copies/ml (IQR: <50-99 copies/ml) in 2006 (trend: $p<0.001$).

Mode of delivery

Most deliveries between 1995 and 2006 were by elective caesarean section (56.4%, 3717/6593). As evidence emerged about the beneficial effects of elective caesarean section in reducing the risk of MTCT (European Collaborative Study, 1994; The European Mode of Delivery Collaboration, 1999), the proportion of elective caesarean sections increased from 38.3% (36/94) in 1997 to a high of 66.4% (144/217) in 1999 (trend: $p<0.001$) (Figure 3.4). Subsequently, the proportion of women delivering by elective caesarean section declined gradually to around 50% (555/1136) in 2006, as advice on the option of vaginal delivery for women with undetectable viral load evolved (BHIVA, 2001; BHIVA, 2005a). Vaginal deliveries increased from 16.6% (36/217) to 28.3% (321/1136) between 1999 and 2006 (trend: $p<0.001$), mostly due to a rise in planned vaginal deliveries (Figure 3.4). The proportion of emergency caesarean sections increased from 17.1% (37/217) in 1999 to 22.9% (260/1136) in 2006 (trend: $p=0.001$); among these, the proportion occurring at 37 weeks gestation or later increased from 48.6% (18/37) in 1999 to 60.6% (155/256) in 2006 (trend: $p=0.021$), suggesting that an increasing proportion of emergency caesarean sections occurred as a result of attempted vaginal deliveries.

Figure 3.4 Mode of delivery by year



N.B. Information on mode of delivery was only collected from 1995 onwards. Information on whether vaginal deliveries were planned was collected from 2002 onwards, but only from obstetric respondents.

Gestational age, birth weight, stillbirth and neonatal death

Median gestational age was 38 weeks (IQR: 38-39 weeks); 14.2% (975/6874) of deliveries were premature (<37 weeks), and 3.6% very premature (<32 weeks). Median birth weight was 3050 g (IQR: 2720-3370 g); 14.1% (827/5865) of infants were of low birth weight (<2500 g) and 3.1% (179/5865) of very of low birth weight (<1500 g). There were no significant trends over time in the proportion of infants who were premature (p=0.564), very premature (p=0.182), of low birth weight (p=0.197) or of very low birth weight (p=0.340). In the general population in the UK, around 6% of babies are born prematurely and a similar proportion are of low birth weight, with no significant trends over time (Maher & Macfarlane, 2004; Moser, Stanfield, & Leon, 2008).

There were 77 stillbirths (11 per 1000 births) and 30 neonatal deaths (4 per 1000 live births). Mortality rates were explored in two time periods (because of small numbers in individual years): the stillbirth rate was similar in 1990-1999 (10 per 1000 births, 10/961) and 2000-2006 (11 per 1000 births, 67/6095, p=0.871). Likewise, there was no significant difference in neonatal mortality rates between the two time periods, although numbers were small: 3 per 1000 live births (3/951) in 1990-1999, and 4 per 1000 live births (27/6028) in 2000-2006 (p=0.562). In the UK overall, the stillbirth rate has remained constant since the mid-1990s, at 5.3 per 1000 births, while neonatal mortality rates declined from 3.9 to 3.4 per 1000 between 2000 and 2006 (Confidential Enquiry into Maternal and Child Health, 2008).

3.3 Mother-to-child transmission

Trends over time (1990-2006)

Infection status was reported for 86.9% (6063/6979) of live births between 1990 and 2006 (those with unreported infection status in 2000-2006 are discussed on page 89). Counting twins as one birth (none were discordant), the overall MTCT rate declined significantly from 18.5% in 1990-1993 (35/189, 95% CI: 13.3-24.8%) to 1.0% (29/2832, 95% CI: 0.7-1.5) in 2004-2006, with a high of 24.1% (13/54, 95% CI: 13.5-37.6%) in 1993 and a low of 0.8% (6/768, 95% CI: 0.3-1.7%) in 2006 (Figure 3.3, page 83). Breastfeeding status was reported for 86.6% (5251/6063) of mothers; the proportion who breastfed their infants declined from 2.9% (5/172) in 1990-1993 to 0.5% (12/2286) in 2004-2006 (trend: p=0.001).

Transmission rates in the HAART era (2000-2006)

Antenatal testing for HIV has been routinely offered and recommended in England since 2000 and in the whole of the UK and Ireland since 2003 (National Institute for Clinical Excellence, 2003; Townsend, Cliffe, & Tookey, 2006). Since 2000 over 80% of HIV-infected pregnant women have been diagnosed by the time of delivery (The UK Collaborative Group for HIV and STI Surveillance, 2006), and of these, over 90% received ART in pregnancy (Figure 3.3, page 83). To explore risk factors for transmission during a period when most HIV-infected women were diagnosed before delivery, and uptake of ART was high, data on singleton infants born between 2000 and 2006 were analysed. Multiple births were excluded from this analysis (n=98); none of the twins or triplets were infected (0/165). Some mothers (n=689)

had two or more pregnancies reported between 2000 and 2006, but none had more than one infected child born during those years.

Maternal characteristics

Most mothers were black African (79%), received antenatal HAART (82%) and delivered by elective caesarean section (57%) (Table 3.4). Median maternal age at delivery was 29.8 years (IQR: 26.2-33.6 years; *n*=5882). Median birth weight was 3051 g (IQR: 2740-3380 g).

Among the 186 women who were untreated in pregnancy, 50 were known to have declined treatment; of the remainder, 43 had been diagnosed late in pregnancy (i.e. less than two weeks prior to delivery) and another 18 had delivered prematurely (12 at <32 weeks, 6 at 33-37 weeks). Among women on HAART, 24.1% (1075/4469) had started treatment before pregnancy (for their own health), and median gestational age at initiation for those starting in pregnancy was 25.9 weeks (IQR: 22.4-28.9 weeks). Initiation of zidovudine monotherapy occurred at a median of 28.0 weeks gestation (IQR: 25.4-30.0 weeks), significantly later than initiation of HAART ($p<0.001$). Median viral load (nearest to delivery) was <50 copies/ml (IQR: <50-184 copies/ml) among women on HAART and 355 copies/ml (IQR: 54-1977 copies/ml) in those on monotherapy; viral load tests were carried out at a median of 70 days (IQR: 35-119 days) and 42 days (IQR: 11-65 days) after initiation of HAART and monotherapy, respectively.

Infants with unreported infection status

Infection status was missing for 13.1% (779/5930) of infants at time of analysis. This was partly due to reporting delay in recent years: infection status was missing for 32.1% (360/1120) of infants born in 2006, but for only 8.7% (419/4810) of those

born between 2000 and 2005. Reasons for unreported infection status were as follows:

1. Birth was only reported through obstetric scheme (no paediatric notification) (54.0%, 421/779);
2. Paediatric follow-up pending (28.4%, 221/779);
3. Child lost to follow-up (11.4%, 89/779);
4. Child left UK/Ireland before infection status established (3.5%, 27/779);
5. Child died before infection status established (most deaths were in premature children or those with congenital abnormalities) (2.7%, 21/779).

Children with unreported infection status did not differ significantly from those with known infection status in terms of maternal HIV exposure group, clinical status or mode of delivery, but more were born at <32 weeks gestation (5.0%, 38/758, versus 2.3%, 115/5002, $p<0.001$), to untreated women (5.9%, 43/733, versus 2.8%, 143/5027, $p<0.001$), and to women with viral load ≥1000 copies/ml (21.8%, 130/596, versus 18.7%, 764/4096, $p=0.061$). These factors tended to be associated: for example, untreated women tended to have higher viral loads, and premature delivery was one of the reasons for remaining untreated at delivery. These children were therefore at higher risk of infection than children for whom infection status was reported, an issue that will be explored later (page 106).

Table 3.4 Characteristics of mother-child pairs for deliveries in 2000-2006

Characteristic (*n*=5930)		***n***	***%***
Maternal ethnic origin (*n*=5875)	White	775	13.2
	Black African	4630	78.8
	Other	470	8.0
Region of birth (*n*=5831)	British Isles	825	14.1
	Sub-Saharan Africa	4531	77.7
	Elsewhere	475	8.2
HIV exposure group (*n*=5930)	Non-injecting drug use *	5689	95.9
	Injecting drug use-associated **	241	4.1
Clinical status (*n*=5134)	Asymptomatic	4606	89.7
	HIV symptoms or AIDS	528	10.3
HIV RNA viral load (*n*=4692)	Undetectable (<50 copies/ml)	2648	56.4
	50-999 copies/ml	1150	24.5
	1000-9999 copies/ml	509	10.8
	≥10,000 copies/ml	385	8.2
CD4 count (*n*=4539)	≥500 cells/µl	1595	35.1
	350-499 cells/µl	1158	25.5
	200-349 cells/µl	1241	27.3
	<200 cells/µl	545	12.0
Antiretroviral therapy (*n*=5760)	Untreated	186	3.8
	Monotherapy	712	12.3
	Dual therapy	136	2.3
	HAART	4726	81.6
Mode of delivery (*n*=5901)	Elective caesarean section	3368	57.1
	Emergency caesarean section	1223	20.7
	Vaginal delivery	1310	22.2
	- planned	*745*	*12.6*
	- unplanned	*176*	*3.0*
	- unspecified	*389*	*6.6*
Gestational age (*n*=5760)	≥37 weeks	5029	87.3
	35-36 weeks	360	6.2
	32-34 weeks	218	3.8
	<32 weeks	153	2.7
Sex of infant (*n*=5903)	Male	2978	50.4
	Female	2925	49.6

* Includes women with missing exposure information. ** Includes women who acquired HIV from a drug-using partner.

Infants with reported infection status

Infection status of the 5151 infants for whom information was provided is shown in Table 3.5; 15% of uninfected children and 25% of infected children had insufficient results at the time of analysis to definitively confirm their infection status (according to the definitions in Chapter 2). Infants with presumed infection status were also included in the analysis to avoid reducing the sample size, and because confirmatory test results hardly ever contradict initial ones (in the NSHPC, this has happened on only two or three occasions over the last 10 years; PA Tookey & J Masters, personal communication).

Table 3.5 Infection status according to receipt of confirmatory results

Infection status	*n*	%
Uninfected		
Confirmed	4328	85.0
Presumed	762	15.0
Infected		
Confirmed	46	75.4
Presumed	15	24.6
Total		
Confirmed	4374	84.9
Presumed	777	15.1

Overall mother-to-child transmission rates

The overall transmission rate was 1.2% (61/5151, 95% CI: 0.9-1.5%). There was a general trend towards lower transmission rates in later years, although it was not statistically significant for individual years (p=0.151) (Table 3.6), or when comparing 2000-2002 (1.6%, 23/1456) with 2003-2006 (1.0%, 38/3695, p=0.069). Transmission was not significantly associated with maternal region of birth or HIV exposure group (Table 3.6). HIV-related symptoms and CD4 cell counts were not

associated with transmission, although there was a slight non-significant trend towards increased transmission at lower CD4 counts (Table 3.6); the lack of association with HIV symptoms is most likely due to small numbers (only seven transmissions in the symptomatic group). Transmission was slightly higher in black African women (1.4%) than in white women (0.4%), although this association was borderline significant (p=0.054). Factors that were significantly associated with transmission in univariable analysis included no maternal ART, vaginal delivery (particularly if unplanned), emergency caesarean section, prematurity (<32 weeks gestation), female sex and detectable viral load (Table 3.7). Restricting the univariable analyses to the subset included in the multivariable models (shown later) did not substantially alter any of the unadjusted odds ratios (data not shown). Table 3.8 shows all infants (and proportion infected) by maternal ART and mode of delivery. Numbers in many of the groups were too small to enable accurate transmission rates to be estimated. Comparison of the most common combinations of ART and mode of delivery are described later (for example, page 103).

Table 3.6 Maternal characteristics and mother-to-child transmission rates

Maternal characteristics (n=5151)*	MTCT rate (%)	(*n* infected / *n* total)	OR (95% CI)	*p*-value
Year of delivery (n=5151)				
2000	1.5	(5 / 327)	-	
2001	1.6	(8 / 485)	-	
2002	1.6	(10 / 644)	-	
2003	1.0	(9 / 901)	-	
2004	1.0	(10 / 989)	-	
2005	1.2	(13 / 1045)	-	*trend*
2006	0.8	(6 / 760)	-	0.151
Ethnic origin (n=5104)				
White	0.4	(3 / 692)	1.00	
Black African	1.4	(54 / 3990)	3.15 (0.98-10.11)	0.054
Other	0.9	(4 / 422)	2.20 (0.49-9.87)	0.304
Region of birth (n=5074)				
British Isles	0.7	(5 / 740)	1.00	
Sub-Saharan Africa	1.4	(54 / 3915)	2.06 (0.82-5.16)	0.125
Elsewhere	0.5	(2 / 419)	0.71 (0.14-3.65)	0.677
HIV exposure group (n=5151)				
Non-injecting drug use	1.2	(60 / 4937)	1.00	
Injecting drug use-associated **	0.5	(1 / 214)	0.38 (0.05-2.77)	0.341
Clinical status (n=4456)				
Asymptomatic	1.1	(45 / 3994)	1.00	
HIV-related symptoms or AIDS	1.5	(7 / 462)	1.35 (0.61-3.01)	0.463
CD4 cell count (n=3962)				
≥500 cells/µl	0.8	(11 / 1389)	1.00	
350-499 cells/µl	1.1	(11 / 1011)	1.38 (0.60-3.19)	0.454
200-349 cells/µl	1.0	(11 / 1080)	1.29 (0.56-2.98)	0.553
<200 cells/µl	1.5	(7 / 482)	1.85 (0.71-4.79)	0.208

* Infants with infection status reported.
** Includes HIV acquisition from a drug-using partner.

Table 3.7 Treatment and pregnancy characteristics and mother-to-child transmission rates

Risk factors (n=5151)*	MTCT rate (%)	(*n* infected / *n* total)	OR (95% CI)	*p*-value
Antiretroviral therapy (n=5027)				
HAART	1.0	(40 / 4120)		
Dual therapy	0.8	(1 / 126)	0.82 (0.11-5.98)	0.841
Monotherapy	0.5	(3 / 638)	0.48 (0.15-1.56)	0.224
None	9.1	(13 / 143)	10.2 (5.33-19.53)	<0.001
Missing	3.2	(4 / 124)		
Mode of delivery (n=5131)				
Elective caesarean section	0.8	(23 / 2953)		
Emergency caesarean section	1.6	(17 / 1056)	2.08 (1.11-3.92)	0.023
Vaginal delivery	1.9	(21 / 1122)	2.43 (1.34-4.41)	0.003
- planned	1.1	(7 / 618)	1.46 (0.62-3.42)	0.384
- unplanned	5.7	(9 / 157)	7.75 (3.52-17.04)	<0.001
- unspecified	1.4	(5 / 347)	1.86 (0.70-4.93)	0.211
Missing	0.0	(0 / 20)		
HIV viral load (n=4096)				
Undetectable (<50 copies/ml)	0.1	(3 / 2309)		
50-999 copies/ml	1.2	(12 / 1023)	9.12 (2.57-32.4)	0.001
1000-9999 copies/ml	1.4	(6 / 429)	10.90 (2.70-43.8)	0.001
≥10,000 copies/ml	6.0	(20 / 335)	48.8 (14.4-165.2)	<0.001
Missing	1.9	(20 / 1055)		
Gestational age (n=5002)				
≥37 weeks	1.0	(45 / 4383)		
35-36 weeks	1.0	(3 / 315)	0.93 (0.29-3.00)	0.899
32-34 weeks	2.1	(4 / 189)	2.08 (0.74-5.86)	0.164
<32 weeks	6.1	(7 / 115)	6.25 (2.75-14.17)	<0.001
Missing	1.3	(2 / 149)		
Sex of infant (n=5141)				
Male	0.9	(22 / 2580)		
Female	1.5	(39 / 2561)	1.80 (1.06-3.04)	0.029
Missing	0.0	(0 / 10)		

* Infants with infection status reported.

Table 3.8 Number of infants and proportion infected by maternal ART and mode of delivery

	Caesarean section						Vaginal delivery									All deliveries		
	Elective			Emergency			Planned			Unplanned			Unspecified					
	Total	*Infected*		*Total*	*Infected*		*Total*	*Infected*		*Total*	*Infected*		*Total*	*Infected*		*Total*	*Infected*	
ART	***n***	***n***	***%***	***n***	***n***	***%***	***n***	***n***	***%***	***n***	***n***	***%***	***n***	***n***	***%***	***n***	***n***	***%***
HAART	2286	17	0.7	877	15	1.7	559	4	0.7	122	4	3.3	263	0	0.0	4107	40	1.0
Dual therapy	69	1	1.4	18	0	0.0	13	0	0.0	2	0	0.0	23	0	0.0	125	1	0.8
Monotherapy	464	0	0.0	108	0	0.0	37	1	2.7	9	1	11.1	19	1	5.3	637	3	0.5
Untreated	52	3	5.8	34	2	5.9	8	2	25.0	24	4	16.7	25	2	8.0	143	13	9.1
Missing	82	2	2.4	19	0	0.0	1	0	0.0	0	0	-	17	2	11.8	119	4	3.4
Total	2953	23	0.8	1056	17	1.6	618	7	1.1	157	9	5.7	347	5	1.4	5131*	61	1.2

* 20 infants with missing information on mode of delivery are excluded from this table, as none were infected.

Multivariable analysis

Because the overall transmission rate was low, there were issues with small numbers, particularly when adjusting for multiple risk factors. Other than mode of delivery and ART, only variables that were significant to $p<0.10$ in a likelihood ratio test (LRT) were included. In the main multivariable logistic regression model adjusting for ART, mode of delivery, gestational age and sex, neither the inclusion of CD4 count nor maternal ethnic group significantly improved the model (LRT, $p=0.490$ and $p=0.145$, respectively). Because of the association between ART and viral load, separate models were developed including and excluding viral load.

In the main model, which included ART, mode of delivery, gestational age and sex (but not viral load) ($n=4892$; Table 3.9), being untreated (AOR=9.08, $p<0.001$) was the strongest risk factor for transmission, and girls were more likely to be infected than boys (AOR=1.91, $p=0.023$). Prematurity (<32 weeks) was a significant risk factor for transmission in the multivariable model (AOR=3.55, $p=0.010$); however, of the seven women who had infected infants born at <32 weeks gestation, all were either untreated ($n=3$) or treated for less than three weeks (range: 1-19 days), and all but one delivered vaginally. Duration of treatment was not included in this model, since this variable did not apply to untreated women. The association between mode of delivery and transmission varied by type of therapy (Table 3.8, page 96), but could not be explored adequately using interaction terms, due to small numbers in many of the cells (Table 3.8); instead, separate analyses by type of ART are presented later.

It was unclear why girls were more likely to be infected than boys. There was no evidence of a differential effect of sex by treatment (any versus none, test of homogeneity of ORs, $p=0.333$) or mode of delivery (test of homogeneity of ORs, $p=0.951$) in this population. There was no evidence of increased fetal death in boys:

in fact, girls were twice as likely to be stillborn as boys (0.98%, 29/2954, versus 0.50%, 15/2993, p=0.031); however, sex was not reported for a third (21/65) of stillbirths in 2000-2006.

Planned versus unplanned vaginal delivery

In the multivariable model, vaginal delivery was associated with a non-significant 1.8-fold increase in transmission compared with elective caesarean section (AOR=1.82, p=0.076). Information on whether vaginal deliveries were planned or unplanned was available for 69.1% (775/1122). After adjusting for ART, gestational age and sex, unplanned vaginal delivery was associated with a significantly increased risk of transmission (AOR=4.16, 95% CI: 1.66-10.41, p=0.002) compared with elective caesarean section, but planned vaginal delivery was not (AOR=1.56, 95% CI: 0.65-3.72, p=0.319).

Viral load

Viral load was reported for 79.5% (4096/5151) of women, but for significantly fewer untreated than treated women (49.7%, 71/143, versus 82.3%, 4021/4884, p<0.001), and infected than uninfected infants (67.2%, 41/61, versus 79.7%, 4055/5090, p=0.024); possible reasons for these patterns include a lack of opportunity for viral load testing in women who present for the first time in labour, and the fact that women who decline ART are likely to refuse viral load testing as well, although no evidence was available to support either of these suggestions. Closest viral load to delivery was measured at a median of 23 days before delivery (IQR: 10-44 days). MTCT increased with increasing viral load, and the association was more pronounced in women who had vaginal deliveries or emergency caesarean sections than in those who delivered by elective caesarean section (Figure 3.5). In multivariable analysis (n=4084) controlling for ART, mode of delivery, gestational

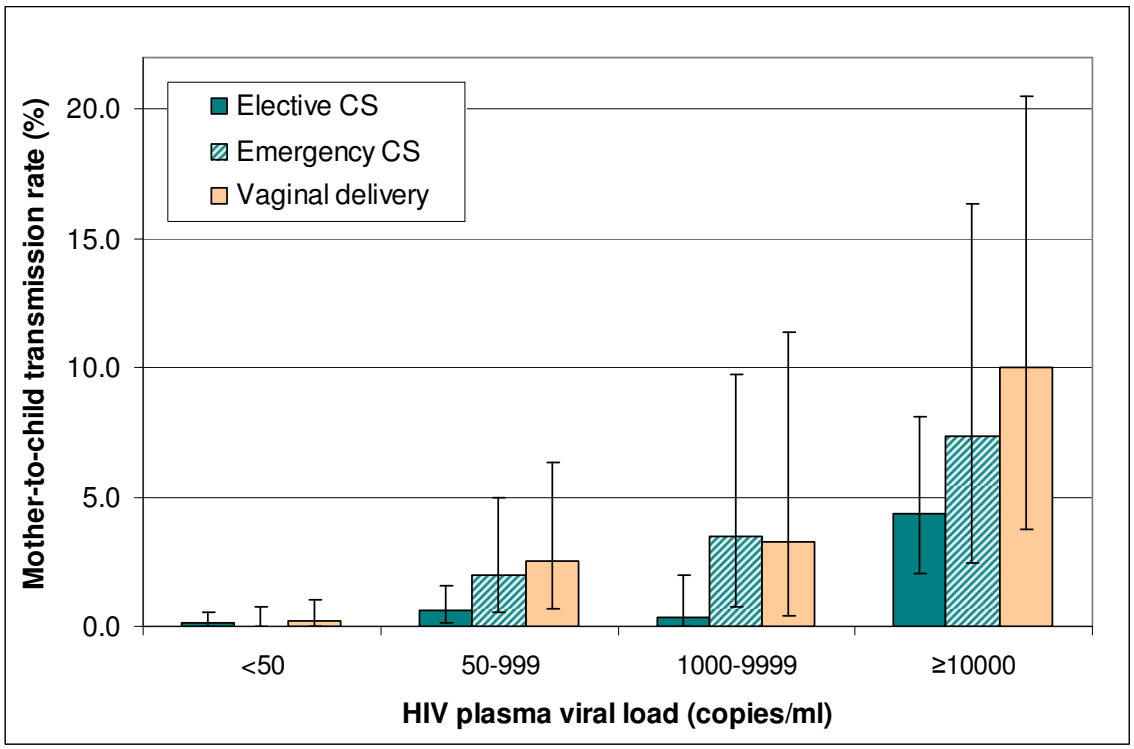
age and sex, each $\log_{10}$ increase in viral load was associated with a 2.4-fold increase in transmission (AOR=2.41, $p<0.001$) (Table 3.9).

In the multivariable model that included viral load, lack of ART (AOR=3.17, $p=0.023$) and vaginal delivery (AOR=2.40, $p=0.033$) were strongly associated with transmission, but gestational age and sex were not (Table 3.9). Adjusting for viral load led to a reduction in the AOR for very premature delivery (<32 weeks) from 3.55 (Model 1) to 2.35 (Model 3), suggesting that at least some of the association between prematurity and transmission was explained by high viral loads in women who delivered prematurely. This is consistent with the observation that the mothers of all seven infected infants born at <32 weeks were on treatment for less than three weeks (or not at all). On the other hand, the reduction in the AOR for the association between female sex and MTCT from 1.91 (Model 1) to 1.58 (Model 3), and loss of statistical significance, was mainly due to the exclusion of 808 mother-child pairs with no viral load information. Indeed, the reduction in the AOR occurred when the analysis was restricted to cases with viral load reported, but without adjusting for viral load (Table 3.9, Model 2).

Table 3.9 Adjusted odds ratios for mother-to-child transmission

	n (model 1)	**Model 1: all cases (*n*=4892), viral load not included**			*n (models 2 & 3)*	**Model 2: cases with viral load reported (*n*=4084), not adjusting for viral load**			**Model 3: cases with viral load reported (*n*=4084), adjusting for viral load**		
		AOR	**95% CI**	***p-value***		**AOR**	**95% CI**	***p-value***	**AOR**	**95% CI**	***p-value***
Antiretroviral therapy											
HAART	4012	1.00			3399	1.00			1.00		
Dual therapy	120	0.86	0.12-6.33	0.883	75	1.60	0.21-11.98	0.647	1.71	0.22-13.03	0.606
Monotherapy	629	0.56	0.17-1.82	0.334	539	0.72	0.22-2.38	0.587	0.57	0.17-1.91	0.366
None	131	9.08	4.54-18.16	<0.001	71	8.58	3.34-22.03	<0.001	3.17	1.17-8.59	0.023
Mode of delivery											
Elective caesarean section	2797	1.00			2399	1.00			1.00		
Emergency caesarean section	1023	1.67	0.80-3.48	0.172	847	1.48	0.62-3.57	0.380	1.89	0.79-4.52	0.153
Vaginal delivery	1072	1.82	0.94-3.53	0.076	838	1.82	0.84-3.93	0.128	2.40	1.08-5.35	0.033
Gestational age											
≥37 weeks	4288	1.00			3584	1.00			1.00		
35-36 weeks	306	0.84	0.25-2.81	0.773	255	0.82	0.19-3.60	0.788	0.49	0.11-2.23	0.359
32-34 weeks	185	1.63	0.54-4.94	0.390	153	1.73	0.47-6.34	0.405	1.17	0.32-4.29	0.816
<32 weeks	113	3.55	1.36-9.30	0.010	92	4.38	1.48-12.99	0.008	2.35	0.77-7.20	0.134
Sex of infant											
Male	2447	1.00			2053	1.00			1.00		
Female	2445	1.91	1.09-3.33	0.023	2031	1.52	0.80-2.87	0.198	1.58	0.82-3.04	0.170
HIV RNA viral load											
Per $\log_{10}$ increase					4084				2.41	1.91-3.05	<0.001

Figure 3.5 Mother-to-child transmission rates (with 95% confidence intervals) by HIV viral load and mode of delivery



Breastfeeding

Although HIV-infected women in the UK and Ireland are recommended to formula feed, breastfeeding was reported in 0.6% (29/4399) of infants with information provided. Three of these infants were infected, all of whom were born to untreated women. Two of the women had declined ART: one breastfed for over three months, and the other's baby was HIV negative at three months and subsequently seroconverted. The third woman had an antenatal HIV test during pregnancy, but the result was not communicated until after delivery; she breastfed for one week, and her baby had a positive DNA PCR test at three weeks of age.

Transmission following HAART

The MTCT rate for women on HAART was 1.0% (40/4120) (Table 3.5). Logistic regression models were developed to explore risk factors for MTCT in this group, but statistical power to detect differences between subgroups was very limited, due to the small number of transmissions. Furthermore, planned, unplanned and unspecified vaginal deliveries had to be combined to avoid omission of subgroups from the models. MTCT rates were not significantly different whether HAART included an NNRTI (0.9%, 18/1959), a PI (1.1%, 20/1795, p=0.625), both an NNRTI and a PI (0.8%, 2/258), or neither (0%, 0/108, p=0.847). Comparing PI with non-PI regimens, there was no difference in MTCT rates after adjusting for mode of delivery, sex and $\log_{10}$ viral load (AOR=1.27, 95% CI: 0.61-2.62, p=0.521; n=3399). Severe prematurity (<32 weeks) was not a significant risk factor for transmission among women on HAART, after adjusting for mode of delivery (vaginal, elective or emergency caesarean section) and sex (AOR=1.32, 95% CI: 0.30-5.82, p=0.714; n=4012), and was therefore omitted from the models.

Timing and duration of HAART

HAART at conception was associated with a significantly lower risk of transmission than HAART started during pregnancy (0.1%, 1/928, versus 1.3%, 39/2967, p=0.001), even after adjusting for mode of delivery and sex (AOR=0.08, 95% CI: 0.01-0.58, p=0.013; n=3880). Adjusting for $\log_{10}$ viral load reduced the magnitude and significance of the association (AOR=0.18, 95% CI: 0.02-1.35, p=0.096; n=3394).

Of the 3192 women who started HAART during pregnancy, date of initiation was available for 2643 (83%); those who transmitted (n=34) started later than those who did not (median gestational age at initiation: 30.1 weeks, IQR: 27.4-32.6 weeks, versus 25.9 weeks, IQR: 22.4-28.7 weeks, p<0.001). In multivariable analysis, each additional completed week of treatment corresponded to a 17% (AOR=0.83, 95% CI: 0.77-0.89, p<0.001; n=2639) reduction in the risk of transmission after adjusting for mode of delivery and sex, and a 10% (AOR=0.89, 95% CI: 0.83-0.96, p=0.003; n=2475) reduction after adjusting for $\log_{10}$ viral load as well as mode of delivery and sex. Most of the decline in transmission occurred in the first six weeks of treatment, with a 43% reduction for each additional week of ART during this period (AOR=0.57, 95% CI: 0.34-0.96, p=0.036; n=278), after adjusting for mode of delivery, sex and $\log_{10}$ viral load.

Elective caesarean section versus planned vaginal delivery

Among women on HAART, there was no statistically significant difference in MTCT rates between elective caesarean section (0.7%, 17/2286) and planned vaginal delivery (0.7%, 4/559; AOR=1.24, 95% CI: 0.34-4.52, p=0.746, adjusted for sex and $\log_{10}$ viral load). Results were similar if women on treatment for less than 14 days were excluded (AOR=1.34, 95% CI: 0.36-5.04, p=0.663), but as with other analyses

among women on HAART, statistical power was limited. Because the BHIVA Guidelines suggest offering planned vaginal deliveries only to women with suppressed viral load on HAART (BHIVA, 2005a), the proportion of women with undetectable viral load was higher in those who had planned vaginal deliveries (79.0%, 417/528) than in those who had elective caesarean sections (58.7%, 1135/1934, $p<0.001$). MTCT rates were higher in women on HAART who had emergency caesarean sections (1.7%, 15/877) or unplanned vaginal deliveries (3.3%, 4/122) compared with those who had elective caesarean section deliveries ($p=0.027$ and $p=0.019$, respectively).

HAART and undetectable viral load

Only three transmissions were reported among 2117 infants born to women on HAART with undetectable viral load (0.1%, 95% CI: 0.0-0.4%); duration of HAART among the mothers who transmitted ranged from 6 to 14 completed weeks. Two of the infants were born by elective caesarean section (0.2%, 2/1135) and one by planned vaginal delivery (0.2%, 1/417); none were premature. Two of the three infants (one born vaginally) had positive HIV PCR tests within 72 hours of birth, suggesting that they were infected *in utero* rather than at the time of delivery (Bryson *et al.*, 1992). The other infant had no PCR tests reported in the first three days of life, and timing of infection was therefore unknown.

Transmission despite interventions

Eighteen other women had infected infants despite HAART and either planned vaginal delivery or elective caesarean section. Ten of them received less than two weeks of treatment and/or had high viral loads near delivery (range: 8500-285,000 copies/ml). In addition, problems with adherence or denial were reported in a few cases, although information was not specifically requested.

There were six transmissions from women with low but detectable viral load (50-999 copies/ml); two had planned vaginal deliveries and four had elective caesarean sections. There was no statistically significant difference in transmission rates between planned vaginal delivery (2.5%, 2/81) and elective caesarean section (0.8%, 4/471, p=0.215) among women with low but detectable viral load, although due to limited statistical power, it was not possible to exclude an effect. Two of these six infected infants had positive HIV PCR tests within 72 hours of birth, suggesting *in utero* transmission (both were born by elective caesarean section). The remaining two of the eighteen women received HAART for at least one month, but no viral loads were reported. Information on neonatal prophylaxis was provided for 20 of the 21 infants infected despite maternal HAART and planned vaginal or elective caesarean section delivery, and all were treated; nine with monotherapy (one zidovudine, one didanosine), three with dual therapy (zidovudine and nevirapine), and eight with triple therapy (mostly combivir and nevirapine). Eighteen infants had breastfeeding status reported, and none were breastfed.

Transmission following zidovudine monotherapy

The mothers of 638 infants received prophylactic zidovudine monotherapy in pregnancy. The majority of these pregnancies were managed in accordance with the BHIVA Guidelines (BHIVA, 2001; BHIVA, 2005a): most of the women had CD4 counts above 200 cells/µl (99% [524/530] including 85% [451/530] above 350 cells/µl) and viral load <10,000 copies/ml (95.7%, 517/540); most (78%) viral loads were measured after initiation of treatment. Seventy three percent (464/637) of women delivered by elective caesarean section.

Three infants were infected (0.5%, 95% CI: 0.1-1.4%); all three mothers were treated with zidovudine for less than one month, had detectable viral load (range: 474-3000

copies/ml) and delivered vaginally (contrary to BHIVA recommendations). The transmission rate following monotherapy and elective caesarean section was 0% (0/464, 95% CI: 0-0.8%), with a median viral load of 400 copies/ml (IQR: 61-1992 copies/ml); this transmission rate was not significantly different from that following HAART and planned vaginal delivery (0.7%) or elective caesarean section (0.7%, Fisher's exact test: p=0.150). The transmission rate following monotherapy and emergency caesarean section was 0% (0/116, 95% CI: 0-3.4%), with a median viral load of 597 copies/ml (IQR: 84-3195 copies/ml); 37% (40/108) of emergency caesarean sections were carried out at <37 weeks gestation, including 5% (5/108) at <32 weeks.

Multiple births

Including all twin and triplet births, or all twin and triplet infants, did not substantially alter the overall MTCT rate (Table 3.10).

Table 3.10 Mother-to-child transmission rates according to inclusion or exclusion of twins and triplets

	Total	*n* infected	MTCT rate (%)	95% CI
Singleton infants only	5151	61	1.18	0.89-1.48
Singletons and first twins/triplets	5233	61	1.17	0.87-1.46
All infants	5316	61	1.15	0.86-1.43

Adjustment for unreported infection status

Potential bias introduced by excluding infants with unreported infection status was investigated by computing likely infection status based on maternal treatment and viral load category. MTCT rates by treatment and viral load are shown in Table 3.11.

Because viral load was unavailable for 50% of untreated women and for almost all women with missing treatment information, the estimated number of additional infected infants in these two groups was calculated using the overall transmission rate for each group (without taking into account viral load): rates were 9.1% for untreated women and 3.2% for those with missing treatment information. Among treated women, transmission rates at different viral load levels were available and were used in the calculations (Table 3.11). Using these transmission rates to compute likely infection status, an estimated 1.4% (11/779) of children with unreported infection status would be infected. The overall transmission rate would remain 1.2% (72/5930, 95% CI: 1.0-1.5%).

A similar result was obtained by imputing probability of infection in Stata, based on ART, mode of delivery (with vaginal delivery classified as planned or unplanned), gestational age groups, infant sex, and $\log_{10}$ viral load. The estimated number of additional infections using this method was 10, with the estimated overall transmission rate remaining 1.2% (71/5930, 95% CI: 0.9-1.5%).

Table 3.11 Mother-to-child transmission rates by maternal antiretroviral therapy and viral load, and estimated number of additional infections among children with unreported infection status

ART	Viral load (copies/ml)	Infected (*n*)	Total (*n*)	Actual MTCT rate (%)	MTCT rate used (%)	Un-reported infection status (*n*)	Estimated additional infected (*n*)
No	<50	0	9	0.0			
	50-999	0	20	0.0			
	1000-9999	0	14	0.0	Numbers too small - overall MTCT rate used in calculation		
	≥10000	6	28	21.4			
	Missing	7	72	9.7			
	Total	**13**	**143**	**9.1**	**9.1**	**43**	**4**
Yes	<50	3	2299	0.1	0.1	337	0
	50-999	12	1003	1.2	1.2	124	1
	1000-9999	6	414	1.4	1.4	72	1
	≥10000	14	305	4.6	4.6	41	2
	Missing	9	863	1.0	1.0	116	1
	Total	**44**	**4884**	**0.9**			
Missing	<50	0	1	0.0			
	50-999	0	0	-			
	1000-9999	0	1	0.0	Numbers too small - overall MTCT rate used in calculation		
	≥10000	0	2	0.0			
	Missing	4	120	3.3			
	Total	**4**	**124**	**3.2**	**3.2**	**46**	**1**
Total		**61**	**5151**	**1.2**		**779**	**11**

3.4 Key points

- The number of pregnancies in diagnosed HIV-infected women in the UK and Ireland increased from around 100 per year in the early 1990s to over 1200 per year from 2005 onwards.
- The demographic profile of HIV-infected pregnant women changed substantially over this period, with a shift in likely route of HIV infection from injecting drug use to exposure in areas of high HIV prevalence, especially sub-Saharan Africa.
- The proportion of women diagnosed antenatally increased in the years following the introduction of routine screening, from less than 40% before 2000, to 60% in 2000-2003.
- The number of pregnancy reports made to the NSHPC increased over time in all parts of the British Isles. The proportion of pregnancies reported from England outside London rose substantially from 13% in 1997-1999 to 43% in 2004-2006.
- The proportion of pregnancy terminations decreased 10-fold between the early 1990s and 2004-2006.
- Uptake of ART increased to 98% in 2006, after zidovudine became available in 1994, and over 80% of women in recent years were on HAART at some time in pregnancy.
- Between 1999 and 2006, the proportion of planned vaginal deliveries rose gradually from 17% to 28%, and the proportion of emergency caesarean sections rose from 17% to 23%.
- MTCT rates declined from a high of 24% in 1993 to 1% in 2004-2006.

- Independent risk factors for transmission in 2000-2006 (when HAART was widely available) included lack of maternal ART, vaginal delivery (particularly if unplanned), female sex, and prematurity (<32 weeks). Viral load remained strongly associated with MTCT.
- The risk of transmission was reduced in women who started HAART before pregnancy (AOR=0.18), compared with those starting during pregnancy. Earlier initiation of HAART was associated with a significant reduction in the risk of transmission (AOR=0.90 per week of treatment) in women who started treatment in pregnancy.
- There was no statistically significant difference in MTCT rates according to the management strategies outlined in the BHIVA Guidelines: HAART with elective caesarean section (0.7%), HAART with planned vaginal delivery (0.7%), or zidovudine monotherapy with elective caesarean section (0%).
- Only three transmissions were reported among 2117 infants born to women on HAART with viral load <50 copies/ml, and two were likely infected *in utero*.

Chapter 4 Antiretroviral therapy, pregnancy complications and congenital abnormalities

The increasing use of antiretroviral therapy (ART) in pregnancy following its success in reducing mother-to-child transmission (MTCT) rates has naturally prompted concerns about potential adverse effects. By reducing HIV RNA viral load and allowing CD4 cell recovery, ART leads to immunological changes which may disrupt those occurring naturally in pregnancy (Fiore *et al.*, 2006), potentially leading to undesirable outcomes such as pre-eclampsia, premature labour or fetal death (European Collaborative Study, 2004a; Suy *et al.*, 2006). In recent years, a substantial minority of women have been on highly active antiretroviral therapy (HAART) at conception and throughout pregnancy, raising additional concerns about possible teratogenic effects associated with fetal exposure in the first trimester of pregnancy, at the time of organogenesis.

Information on pregnancy outcome (miscarriage, stillbirth and neonatal death) and congenital abnormality has been routinely collected through the National Study of HIV in Pregnancy and Childhood (NSHPC) since its inception. In addition, in response to concerns raised about ART and pre-eclampsia (Suy *et al.*, 2004; Suy *et al.*, 2006), information on pregnancy complications, including pre-eclampsia, was collected from mid-2004 onwards.

In this chapter the association between ART and adverse pregnancy and perinatal outcomes is explored; the first section addresses stillbirths and neonatal deaths; the second section, pregnancy complications; and the third section, congenital abnormalities, particularly in relation to timing of ART exposure. Information on congenital abnormality rates in the NSHPC between 1990 and 2003 was initially

published in 2006 (Townsend *et al.*, 2006) (Appendix 2, page 365). An updated analysis using data for 1990 to 2007 was published in 2009 (Townsend *et al.*, 2009) (Appendix 2, page 333) and relates to results shown here. The association between ART and premature delivery will be explored in detail in Chapter 5.

4.1 Methods

In this chapter, clinical status refers to HIV-related symptoms or AIDS occurring at any time in pregnancy.

Stillbirth and neonatal death

Analysis of stillbirth and neonatal death was based on births between 1990 and 2007, reported to the NSHPC by June 2008; twin births were included and were defined as a stillbirth if one or both twins died. Because the lowest stillbirth rate was in women on monotherapy, this group was chosen as the baseline for comparison by type of ART.

Pregnancy complications

Analysis of pregnancy complications was restricted to pregnancies delivered between 2004 and 2007, for which information on complications was sought. Information was collected from obstetric respondents only, and was recorded on the database as reported. Details of laboratory tests and criteria for establishing diagnosis were not available. Known risk factors for pre-eclampsia on which information was available through the NSHPC were maternal age, clinical status and multiple pregnancy (Sibai, Dekker, & Kupferminc, 2005). Since the dataset was restricted to pregnancies delivered between 2004 and 2007, only a small proportion (6%, 210/3567) were second or third pregnancies in women already reported with one pregnancy during

that period. Only six women had pregnancy complications reported in two pregnancies included in the dataset, so logistic regression analyses were not adjusted for repeat pregnancies. In these analyses, monotherapy was chosen as the baseline for comparison of type of ART, due to the small number of pregnancies (*n*=53) in untreated women.

Congenital Abnormalities

This analysis included all infants (live born, stillborn, twins and triplets) born between 1990 and 2007 in the UK and Ireland to women diagnosed before delivery and reported to the NSHPC by June 2008. Congenital abnormality rates and 95% confidence intervals (CI) were calculated, overall and by timing and type of ART in pregnancy. First trimester ART exposure was classified according to class, but not number, of antiretroviral drugs included (since few women were on monotherapy or dual therapy in early pregnancy). The four ART categories were: nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or both NNRTI and PI; regimens in the latter three categories could also include NRTIs. Because of specific concerns (detailed in Chapter 1), abnormality rates were calculated for infants exposed to efavirenz or didanosine in early pregnancy, and the rate of hypospadias was explored by ART exposure. Potential confounders on which information was available included maternal ethnicity, age, injecting drug use (as the reported route of HIV acquisition) and clinical status (EUROCAT, 2004).

4.2 Stillbirths and neonatal deaths

Out of the 8430 births reported for 1990-2007, 92 were stillbirths, and there were 30 neonatal deaths. Three women had two stillbirths reported during the study period, but none had more than one infant who died neonatally. The stillbirth rate was 10.9 per 1000 births (92/8430) (95% CI: 8.8-13.4), compared with a UK population rate of 5.3 per 1000 births (95% CI: 5.1-5.5) in 2006 (Confidential Enquiry into Maternal and Child Health, 2008). The neonatal mortality rate was 3.6 per 1000 live births (30/8338) (95% CI: 2.4-5.1), in line with population rates of 3.9 per 1000 (95% CI: 3.7-4.0) in 2000 and 3.4 per 1000 (95% CI: 3.3-3.6) in 2006 (Confidential Enquiry into Maternal and Child Health, 2008). Fifteen of the neonatal deaths occurred before the seventh day of life; the perinatal mortality rate was 12.7 per 1000 births (107/8430) (95% CI: 10.4-15.3).

For over half the stillbirths, details were provided on likely cause of death (Table 4.1). Reasons reported included placental problems (insufficiency, abruption) (15.2% of all stillbirths), perinatal infections (8.7%), congenital abnormalities (7.6%) and pre-eclampsia (5.4%) (Table 4.1). In the general population, congenital abnormality is reported as the most common cause of stillbirth (15%), followed by antepartum haemorrhage (10%), intrapartum causes (7%), pre-eclampsia (4%) and infection (2%) (Confidential Enquiry into Maternal and Child Health, 2006). Because information is not specifically requested on cause of death in the NSHPC, it is possible that reasons were identified in some of the cases where no information was supplied, although in general, at a population level, about half of all stillbirths remain unexplained (Confidential Enquiry into Maternal and Child Health, 2006).

Table 4.1 Reasons or complications reported for stillbirths

Reason / complication reported	*n*	%
Placental insufficiency or abruption	14	15.2
Perinatal infection	8	8.7
Congenital abnormality	7	7.6
Pre-eclampsia	5	5.4
Hypertension or proteinuria	5	5.4
Multiple pregnancy	3	3.3
Delivery complications	2	2.2
Maternal death near delivery	1	1.1
No apparent cause identified	6	6.5
Intrauterine death, no further details	10	10.9
No details supplied	31	33.7
Total	**92**	**100.0**

Stillbirth rates by maternal and pregnancy characteristics are shown in Table 4.2. Multiple pregnancy was associated with a 2.7-fold increased risk of stillbirth, and CD4 count <200 cells/µl with a two-fold increase. Untreated women were almost nine times more likely than women on monotherapy to have a stillborn child (p<0.001), although in this analysis this was mainly because these stillbirths occurred very early, most likely before treatment could be initiated; 10 out of 14 occurred at <32 weeks gestation, including eight at <28 weeks gestation.

Stillbirth was four times more likely in women on HAART than in those on monotherapy (p=0.019). In multivariable analysis (n=6345), adjusting for CD4 cell count and multiple pregnancy, HAART remained associated with stillbirth, although this was only borderline significant, likely due to the small number of stillbirths in some of the cells (adjusted odds ratio [AOR]=3.13, 95% CI: 0.98-10.00, p=0.055). In the multivariable model, CD4 count <200 cells/µl was significantly associated with stillbirth compared with CD4 ≥500 cells/µl (AOR=1.79, 95% CI: 1.03-3.13, p=0.041) but the association with multiple pregnancy was no longer significant (AOR=2.37, 95% CI: 0.73-7.67, p=0.150, for multiple versus singleton pregnancies); since the AOR was similar to the odds ratio (OR), the lack of statistical significance was likely due to small numbers.

Table 4.2 Stillbirth rates and unadjusted odds ratios by maternal demographic and pregnancy characteristics

	Total	Pregnancy complication			*p* -value
		n	%	OR (95% CI)	
Timing of diagnosis (n=8320)					
Before this pregnancy	4222	51	1.2	1.00	
During this pregnancy	4098	41	1.0	0.83 (0.55-1.25)	0.366
Exposure category (n=8430)					
Non-injecting drug use	8050	89	1.1	1.00	
Injecting drug use	380	3	0.8	0.71 (0.22-2.26)	0.564
Ethnic group (n=8351)					
White	1317	12	0.9	1.00	
Black African	6375	71	1.1	1.22 (0.66-2.26)	0.518
Other	659	9	1.4	1.51 (0.63-3.59)	0.356
Age at delivery (n=8365)					
<20 years	276	3	1.1	0.95 (0.29-3.11)	0.926
20-24 years	1232	12	1.0	0.85 (0.43-1.65)	0.625
25-29 years	2698	31	1.1	1.00	
30-34 years	2587	26	1.0	0.87 (0.52-1.48)	0.613
35-39 years	1347	15	1.1	0.97 (0.52-1.80)	0.920
≥40 years	225	5	2.2	1.96 (0.75-5.08)	0.169
Parity (live/stillbirths) (n=5477)					
0	1973	24	1.2	1.00	
1	1810	18	1.0	0.82 (0.44-1.51)	0.516
2	976	11	1.1	0.93 (0.45-1.90)	0.833
3 or more	718	9	1.3	1.03 (0.48-2.23)	0.938
Clinical status (n=7385)					
Asymptomatic	6574	78	1.2	1.00	
HIV symptoms or AIDS	811	13	1.6	1.36 (0.75-2.45)	0.312
CD4 cell count (n=6351)					
≥500 cells/µl	2154	21	1.0	1.00	
350-499 cells/µl	1714	25	1.5	1.50 (0.84-2.70)	0.171
200-349 cells/µl	1717	17	1.0	1.02 (0.53-1.93)	0.962
<200 cells/µl	766	16	2.1	2.17 (1.12-4.17)	0.021
Multiple pregnancy (n=8430)					
Singleton	8288	88	1.1	1.00	
Twin / triplet	142	4	2.8	2.70 (0.98-7.46)	0.055
ART (n=8171)					
Untreated	574	14	2.4	8.82 (2.52-30.81)	0.001
Monotherapy	1061	3	0.3	1.00	
Dual therapy	223	2	0.9	3.19 (0.53-19.21)	0.205
HAART	6313	70	1.1	4.01 (1.26-12.76)	0.019
- *without PI*	2714	38	1.4	5.01 (1.54-16.26)	0.007
- *with PI*	3585	32	0.9	3.18 (0.97-10.39)	0.056

4.3 Pregnancy complications

All complications

The following analysis is restricted to 3852 pregnancies delivered between 2004 and 2007. This subset comprised 45.7% (3852/8430) of all reported births, and 80% (3852/4820) of all births between 2004 and 2007; of the 968 births between 2004 and 2007 for which information on complications was not sought, 40% (383/968) were reported on an earlier version of the data collection form (which did not solicit the information required), and 60% (585/968) through paediatric respondents only (who were not asked to provide the information). The question on pregnancy complications was completed for 92.6% of pregnancies (3567/3852), and of those, problems were reported in 7.7% (275/3567) (Table 4.3). The most commonly reported problems were pre-eclampsia (2.1% overall), hypertension (1.3%) and gestational diabetes (0.9% overall) (Table 4.3). Rates were generally lower than expected, with pre-eclampsia occurring in 2-7% of pregnancies in the general population (Sibai, Dekker, & Kupferminc, 2005), and gestational diabetes in about 3.5% (National Institute for Clinical Excellence, 2008). Pregnancy outcomes included 64 multiple pregnancies, 40 stillbirths, and 11 neonatal deaths.

Missing information on pregnancy problems

Information on pregnancy complications was missing for 7.4% (285/3852) of pregnancies; these were more likely to be in women who acquired HIV through injecting drug use (14.1%, 10/71, versus 7.3%, 275/3781, p=0.030), in untreated women (15.9%, 10/63, versus 7.1%, 268/3766, p=0.008) and in those with lower CD4 count (8.9%, 33/369, for CD4<200 cells/µl, versus 5.3%, 68/1277, for CD4

≥500 cells/μl, p=0.011). There was no significant association between availability of information and any other variable (timing of diagnosis, ethnic group, maternal age, parity, clinical status, mode of delivery or multiple pregnancy).

Pregnancy and perinatal outcomes

Compared with pregnancies with no complications reported, those with problems were more likely to result in emergency caesarean section delivery (51% versus 21%), premature delivery (46% versus 11%), stillbirth (7% versus 0.5%), and an infant with a congenital abnormality (5% versus 2%) (Table 4.4). Pregnancy complications were reported in 53.0% of stillbirths (18/34), and 2 of 10 pregnancies resulting in a neonatal death.

Table 4.3 Prevalence of pregnancy complications in the NSHPC

Category	Pregnancy complication	*n*	%
None		3292	92.3
Hypertensive conditions	Hypertension	48	1.3
	Pregnancy-induced hypertension	17	0.5
	Proteinuria	2	0.1
	Pre-eclampsia *	72	2.0
	HELLP syndrome	2	0.1
	Pre-eclampsia and gestational diabetes	2	0.1
Diabetes	Diabetes	4	0.1
	Gestational diabetes **	30	0.8
Obstetric complications	Placental problems	20	0.6
	Oligohydramnios/low liquor	4	0.1
	Polyhydramnios	7	0.2
	Post-partum haemorrhage	3	0.1
	Intra-uterine growth retardation	15	0.4
Haematological problems	Anaemia	7	0.2
	Thrombocytopaenia/low platelets	5	0.1
	Thrombosis (DVT/embolism)	5	0.1
Liver / cholesterol	Abnormal LFTs/liver abnormalities	6	0.2
	Obstetric cholestasis	10	0.3
	Cholesterol problems	2	0.1
Other	Nephrotic syndrome/renal failure	4	0.1
	Other specified problems ***	10	0.3
Total		**3567**	**100.0**

DVT, deep vein thrombosis; HELLP, haemolysis, elevated liver enzymes or low platelet counts; LFT, liver function tests.
* The overall rate of pre-eclampsia (2.1%) included women who also had gestational diabetes reported (*n*=2), and those with HEELP syndrome (*n*=2). ** Likewise, the overall rate of gestational diabetes (0.9%) included women who also had pre-eclampsia reported.
*** Including antepartum bleeding/haemorrhage (*n*=4), abdominal pain (*n*=2), oesophageal varices, motor neurone palsy, fibroid uterus, thyrotoxicosis, seizure.

Table 4.4 Pregnancy and perinatal characteristics by report of pregnancy complications

	No complications		Complications		*p*-value (exact)
	%	*n*	%	*n*	
Outcome (n=3567)					
Live birth	99.5	3276	93.5	257	
Stillbirth	0.5	16	6.5	18	<0.001
Mode of delivery (n=3562)					
Elective caesarean section	51.6	1698	28.0	77	
Emergency caesarean section	21.4	704	51.3	141	
Vaginal	27.0	889	19.3	53	<0.001
Gestational age (n=3567)					
≥37 weeks	89.3	2939	53.8	148	
35-36 weeks	5.5	182	17.5	48	
32-34 weeks	2.9	94	12.0	33	
<32 weeks	2.3	77	16.7	46	<0.001
Birth weight (n=3470)					
≥2500 g	85.5	2815	52.0	143	
1500-2499 g	9.7	319	27.3	75	
<1500 g	2.1	70	17.5	48	<0.001
Sex of child (n=3552)					
Male	50.7	1670	46.2	127	
Female	48.8	1608	53.5	147	0.148
Congenital abnormality (n=3536)					
No	97.5	3209	90.9	250	
Yes	1.9	63	5.1	14	0.001
Child's HIV infection status (n=2817)					
Uninfected	78.4	2580	77.1	212	
Infected	0.8	25	0.0	0	0.254
Neonatal death (n=3567)					
No	99.8	3284	99.3	273	
Yes	0.2	8	0.7	2	0.177

Risk factors for pregnancy complications

Pregnancy complications (of any kind) were more common in women who were older (14% for women over 44, versus 4% for those under 20 years of age), symptomatic (14%, versus 7% in asymptomatic women), had CD4 counts <200 cells/μl (12%, versus 7% for CD4 ≥500 cells/μl) or a history of three or more previous births (12%, versus 7% for nulliparous women), as well as in multiple pregnancies (19% versus 7.5%) (Table 4.5). Pregnancy complication rates were also higher in women on HAART regimens that did not contain PIs, compared with monotherapy (OR=1.85), although this was only of borderline significance (p=0.052).

Variables that were significantly associated with pregnancy complications in univariable analysis were included in a multivariable logistic regression model. Maternal age, clinical status, CD4 cell count and multiple pregnancy were all significantly and independently associated with pregnancy complications, after adjusting for all other factors including parity and ART (Table 4.6). After adjusting for these other variables, in particular maternal age, parity was no longer a risk factor for pregnancy complications. Non-PI HAART was also no longer significantly associated with pregnancy problems; the OR for non-PI HAART versus monotherapy was reduced after adjusting for both HIV-related symptoms (AOR=1.3, adjusting only for symptoms) and CD4 count (AOR=1.3, adjusting only for CD4 count), suggesting that the observed effect was due to confounding by maternal clinical factors associated with type of ART. Indeed, very few women on monotherapy were symptomatic (1.7%, 4/235), and among those on HAART, symptoms were more common in women on non-PI-based HAART (14.2%, 143/1004) than in those on PI-based HAART (7.9%, 193/2428, p<0.001).

Among women on HAART the risk of pregnancy complications was higher in those who were on treatment at the time of conception than in those who started HAART in pregnancy (11.2%, 103/917, versus 6.5%, 151/2310; OR=1.81, 95% CI: 1.39-2.35, $p<0.001$). Because timing of treatment only applied to women on HAART, this variable could not be included in the main multivariable model. However, in a separate model restricted to women on HAART ($n=2523$), pregnancy complications remained significantly associated with HAART at conception after adjusting for maternal age, parity, clinical status, CD4 cell count and multiple pregnancy: AOR=1.79 (95% CI: 1.30-2.46, $p<0.001$). This association was mainly due to increased rates of hypertensive conditions (including pre-eclampsia) in women on HAART at conception (5.7%, 52/917) compared with those on HAART later (3.3%, 77/2310, $p=0.002$). The association was reduced and no longer significant after excluding hypertensive conditions (AOR=1.48, 95% CI: 0.94-2.32, $p=0.087$), although this could have been due to smaller numbers.

Table 4.5 Pregnancy complication rates and unadjusted odds ratios by maternal demographic and pregnancy characteristics

	Total	Pregnancy complication			*p* -value
		n	%	OR (95% CI)	
Timing of diagnosis (n=3564)					
Before this pregnancy	1939	164	8.5	1.00	
During this pregnancy	1625	111	6.8	0.79 (0.62-1.02)	0.070
Exposure category (n=3567)					
Non-injecting drug use	3506	272	7.8	1.00	
Injecting drug use	61	3	4.9	0.61 (0.19-1.98)	0.414
Ethnic group (n=3561)					
White	444	33	7.4	1.00	
Black African	2803	222	7.9	1.07 (0.73-1.57)	0.723
Other	314	20	6.4	0.85 (0.48-1.51)	0.572
Age at delivery (n=3567)					
<20 years	118	5	4.2	0.67 (0.27-1.71)	0.405
20-24 years	464	25	5.4	0.87 (0.54-1.39)	0.555
25-29 years	1071	66	6.2	1.00	
30-34 years	1108	88	7.9	1.31 (0.94-1.83)	0.106
35-39 years	682	74	10.9	1.85 (1.31-2.62)	0.000
≥40 years	124	17	13.7	2.42 (1.37-4.27)	0.002
Parity (live/stillbirths) (n=2913)					
0	1132	86	7.6	1.00	
1	965	68	7.0	0.92 (0.66-1.28)	0.630
2	496	39	7.9	1.04 (0.70-1.54)	0.853
3 or more	320	38	11.9	1.64 (1.09-2.45)	0.016
Clinical status (n=3529)					
Asymptomatic	3206	228	7.1	1.00	
HIV symptoms or AIDS	323	45	13.9	2.11 (1.50-2.98)	<0.001
CD4 cell count (n=3361)					
≥500 cells/µl	1209	81	6.7	1.00	
350-499 cells/µl	933	69	7.4	1.11 (0.80-1.55)	0.532
200-349 cells/µl	883	67	7.6	1.14 (0.82-1.60)	0.434
<200 cells/µl	336	40	11.9	1.88 (1.26-2.81)	0.002
Multiple pregnancy (n=3567)					
Singleton	3509	264	7.5	1.00	
Twin / triplet	58	11	19.0	2.88 (1.47-5.61)	0.002
ART (n=3538)					
Untreated	53	4	7.5	1.40 (0.43-4.53)	0.573
Monotherapy	218	12	5.5	1.00	
Dual therapy	38	2	5.3	0.95 (0.20-4.44)	0.952
HAART	3229	254	7.9	1.47 (0.81-2.66)	0.209
- without PI	946	92	9.7	1.85 (0.99-3.44)	0.052
- with PI	2283	162	7.1	1.31 (0.72-2.40)	0.379

Table 4.6 Pregnancy problems: unadjusted and adjusted odds ratios by maternal characteristics

		Univariable (*n*=2749) **			Multivariable (*n*=2749) ***		
	n	**OR**	**(95% CI)**	***p*-value**	**AOR**	**(95% CI)**	***p*-value**
Age at delivery							
per year	2749	1.06	(1.03-1.09)	<0.001	1.05	(1.02-1.08)	<0.001
Parity (live/stillbirths)							
0	1075	1.00			1.00		
1	902	0.86	(0.61-1.22)	0.403	0.76	(0.53-1.09)	0.136
2	467	1.01	(0.67-1.52)	0.956	0.77	(0.50-1.18)	0.225
3 or more	305	1.62	(1.07-2.45)	0.022	1.13	(0.72-1.79)	0.588
Clinical status							
Asymptomatic	2484	1.00			1.00		
Symptomatic *	265	2.04	(1.39-2.99)	<0.001	1.65	(1.10-2.45)	0.014
CD4 count							
≥500 cells/µl	986	1.00			1.00		
350-499 cells/µl	769	0.98	(0.67-1.42)	0.912	0.90	(0.62-1.32)	0.587
200-349 cells/µl	720	1.16	(0.81-1.67)	0.425	0.99	(0.68-1.44)	0.959
<200 cells/µl	274	2.11	(1.38-3.22)	0.001	1.70	(1.09-2.64)	0.019
Multiple pregnancy							
Singleton	2702	1.00			1.00		
Twin / triplet	47	2.88	(1.38-6.05)	0.005	2.74	(1.29-5.84)	0.009
Type of ART							
Untreated	27	3.21	(0.91-11.26)	0.069	3.01	(0.85-10.66)	0.088
Monotherapy	175	1.00			1.00		
Dual therapy	25	1.60	(0.33-7.89)	0.561	1.26	(0.25-6.33)	0.781
HAART	2522	1.58	(0.80-3.14)	0.191	1.27	(0.63-2.56)	0.497
- *without PI*	717	2.19	(1.07-4.46)	0.031	1.65	(0.79-3.42)	0.181
- *with PI*	1805	1.35	(0.67-2.70)	0.399	1.16	(0.57-2.34)	0.687

* HIV-related symptoms or AIDS
** Univariable analysis for cases included in the multivariable model (*n*=2749)
*** Multivariable analysis based on ART variable with PI and non-PI HAART; the combined HAART category was added separately.

Pre-eclampsia

Pre-eclampsia was reported in 2.1% (76/3567) of pregnancies, which is on the low end of the 2-7% range reported for the wider population (Sibai, Dekker, & Kupferminc, 2005). Seventy percent (53/76) of pregnancies with pre-eclampsia were delivered prematurely, including 27% (20/76) before 32 weeks, and pre-eclampsia was present in 11% (53/480) of all premature deliveries. In five percent (4/76) of pregnancies with pre-eclampsia, the outcome was a stillbirth; none of the live born infants died neonatally.

Pre-eclampsia rates were higher in women with known risk factors, but this was not statistically significant for maternal age, parity and multiple pregnancy, probably due to small numbers (Table 4.7). Pre-eclampsia rates were higher in women who were symptomatic (p=0.041) or had CD4 counts <200 cells/µl (p=0.063 for comparison with CD4≥200 cells/µl, and p=0.038 for comparison with CD4≥500 cells/µl). Pre-eclampsia was not significantly associated with type of ART overall (Table 4.7).

Because of specific concerns about pre-eclampsia risk in women on HAART at conception (Suy *et al.*, 2004), the association between type and timing of HAART and pre-eclampsia was explored. Crude pre-eclampsia rates were 2.7% (12/424) in women on PI-based HAART at conception, 2.9% (14/466) in those on non-PI HAART at conception, 2.8% (13/466) in those starting a non-PI regimen in pregnancy, and 1.6% (30/1843) in those starting a PI regimen in pregnancy.

Table 4.7 Pre-eclampsia rates and unadjusted odds ratios by maternal demographic and pregnancy characteristics

		Pre-eclampsia				
	Total	***n***	**%**	**OR**	**(95% CI)**	***p* -value**
Timing of diagnosis (n=3564)						
Before this pregnancy	1939	47	2.4	1.00		
During this pregnancy	1625	29	1.8	0.73	(0.46-1.17)	0.190
Exposure category (n=3567)						
Non-injecting drug use	3506	76	2.2	NA		
Injecting drug use	61	0	0.0	NA		
Ethnic group (n=3561)						
White	444	8	1.8	1.00		
Black African	2803	62	2.2	1.23	(0.59-2.59)	0.581
Other	314	6	1.9	1.06	(0.36-3.09)	0.913
Age at delivery (years) (n=3567)						
<20 years	118	1	0.8	0.41	(0.05-3.05)	0.382
20-24 years	464	9	1.9	0.94	(0.43-2.06)	0.884
25-29 years	1071	22	2.1	1.00		
30-34 years	1108	27	2.4	1.19	(0.67-2.10)	0.547
35-39 years	682	13	1.9	0.93	(0.46-1.85)	0.829
≥40 years	124	4	3.2	1.59	(0.54-4.69)	0.401
Parity (live/stillbirths) (n=2913)						
0	1132	33	2.9	1.00		
1	965	15	1.6	0.53	(0.28-0.97)	0.041
2	496	10	2.0	0.69	(0.34-1.40)	0.300
3 or more	320	7	2.2	0.74	(0.33-1.70)	0.484
Clinical status (n=3529)						
Asymptomatic	3206	63	2.0	1.00		
HIV symptoms or AIDS	323	12	3.7	1.92	(1.03-3.61)	0.041
CD4 cell count (n=3361)						
≥500 cells/µl	1209	23	1.9	1.00		
350-499 cells/µl	933	18	1.9	1.01	(0.54-1.89)	0.964
200-349 cells/µl	883	16	1.8	0.95	(0.50-1.81)	0.880
<200 cells/µl	336	13	3.9	2.08	(1.04-4.14)	0.038
Multiple pregnancy (n=3567)						
Singleton	3509	73	2.1	1.00		
Twin / triplet	58	3	5.2	2.57	(0.79-8.40)	0.119
ART (n=3538)						
Untreated	53	1	1.9	1.03	(0.11-9.40)	0.980
Monotherapy	218	4	1.8	1.00		
Dual therapy	38	1	2.6	1.45	(0.16-13.30)	0.745
HAART	3229	69	2.1	1.17	(0.42-3.23)	0.765
- without PI	946	27	2.9	1.57	(0.54-4.54)	0.403
- with PI	2283	42	1.8	1.00	(0.36-2.82)	0.996

NA, not applicable.

HAART started before pregnancy was less likely to contain PIs (47.2%, 463/980) than HAART started during pregnancy (79.7%, 1980/2484, $p<0.001$), reflecting the selective use of nevirapine (an NNRTI) for women with CD4 counts <250 cells/μl. PI-based HAART started in pregnancy was initiated slightly later (median 24.7 weeks, IQR: 21.9-28.0 weeks) than non-PI HAART (23.5 weeks, IQR: 20.6-27.1 weeks, $p<0.001$).

Multivariable logistic regression models were fitted, adjusting for known risk factors on which information was available. Because of the small numbers involved, parity and CD4 count were recoded as binary variables (any or no previous live/stillbirth(s); CD4 count <200 cells/μl or ≥ 200 cells/μl) and maternal age was included as a continuous variable. CD4 count <200 cells/μl was associated with a two-fold increase in pre-eclampsia compared with CD4 count ≥200 cells/μl, and having had one or more previous deliveries was associated with a significantly lower risk of pre-eclampsia (AOR=0.55) (Table 4.8). Clinical status and multiple pregnancy were not significantly associated with pre-eclampsia. The risk of pre-eclampsia was 1.7 times higher in women on non-PI-based HAART compared with PI-based HAART, and 1.6-fold higher if HAART was initiated prior to conception, but neither association was statistically significant (Table 4.8). Despite the fact that these two associations were driven by the low pre-eclampsia rate in women starting PI-based HAART in pregnancy, there was no statistically significant evidence of interaction between type and timing of HAART (test of homogeneity of ORs: $p=0.345$) although this could be due to the limited power of the test.

Although PI-based HAART was started later in pregnancy, the (non-significant) association between type of HAART and pre-eclampsia remained after adjusting for gestation week at initiation (AOR=2.01, 95% CI: 0.91-4.44, $p=0.085$; $n=1759$). Starting HAART later was associated with a 6% decrease in the risk of pre-eclampsia

(AOR=0.94, 95% CI: 0.88-1.00, p=0.069) for each week of gestation, after adjusting for type of regimen, parity and CD4 count (excluding clinical status and multiple pregnancy). There was, however, weak evidence of an interaction between CD4 count and HAART: the association between pre-eclampsia and both type and timing of HAART were apparent only in women with CD4 counts above 200 cells/μl (test of homogeneity of ORs: p=0.152 and p=0.107 for type and timing of ART, respectively) (Table 4.9). In multivariable analysis restricted to women on HAART with CD4 counts ≥200 cells/μl and including type and timing of HAART and parity (n=2272), HAART at conception was associated with a significant 2.3-fold increase in pre-eclampsia compared with HAART later in pregnancy (95% CI: 1.16-4.55, p=0.017); the association with non-PI HAART was reduced in magnitude and not significant (AOR=1.63, 95% CI: 0.84-3.19, p=0.152).

Similar results were obtained when the outcome included cases of pregnancy-induced hypertension (n=16) or any hypertension (n=58). The only important difference was a significant association with maternal age (AOR=1.05 per year, 95% CI: 1.01-1.10, p=0.010) when any hypertension was included, consistent with the known correlation between age and blood pressure (Ong *et al.*, 2007).

Table 4.8 Unadjusted and adjusted odds ratios for pre-eclampsia in women on HAART

		Univariable (*n*=3231)			Multivariable (*n*=2522)		
	n	**OR**	**(95% CI)**	***p*-value**	**AOR**	**(95% CI)**	***p*-value**
Type of HAART							
- with PI	2283	1.00			1.00		
- without PI	946	1.57	(0.96-2.56)	0.072	1.75	(0.95-3.22)	0.072
HAART initiation							
During pregnancy	2310	1.00			1.00		
Before pregnancy	917	1.54	(0.94-2.52)	0.087	1.62	(0.91-2.88)	0.099
Maternal age							
Per year	3231	1.02	(0.98-1.06)	0.381	1.02	(0.97-1.08)	0.378
Parity (live/stillbirths)							
0	1035	1.00			1.00		
1 or more	1609	0.66	(0.39-1.10)	0.114	0.50	(0.28-0.90)	0.020
Clinical status							
Asymptomatic	2885	1.00			1.00		
HIV symptoms or AIDS	317	1.99	(1.05-3.75)	0.034	1.46	(0.71-3.01)	0.302
CD4 count							
≥200 cells/µl	2758	1.00			1.00		
<200 cells/µl	326	1.78	(0.92-3.45)	0.086	2.09	(1.04-4.17)	0.037
Multiple pregnancy							
Singleton	3176	1.00			1.00		
Twin / triplet	55	2.72	(0.83-8.93)	0.099	1.96	(0.45-8.47)	0.366

Table 4.9 Type and timing of HAART and pre-eclampsia: rates and unadjusted odds ratios stratified by CD4 cell count

		Pre-eclampsia				
	n	***n***	**%**	**OR**	**(95% CI)**	***p*-value**
CD4≥200 cells/µl						
Type of HAART						
- with PI	1969	30	1.5	1.00		
- without PI	789	23	2.9	1.94	(1.12-3.36)	0.018
HAART initiation						
During pregnancy	1997	31	1.6	1.00		
Before pregnancy	760	22	2.9	1.89	(1.09-3.29)	0.024
CD4<200 cells/µl						
Type of HAART						
HAART with PI	233	8	3.4	1.00		
HAART without PI	93	3	3.2	0.94	(0.24-3.61)	0.925
HAART initiation						
During pregnancy	186	6	3.2	1.00		
Before pregnancy	140	5	3.6	1.11	(0.33-3.72)	0.864

Gestational diabetes

Gestational diabetes was reported in only 0.8% of pregnancies (30/3567, Table 4.3), and in a higher proportion of women on non-PI HAART (1.4%, 13/946) than PI-based HAART (0.7%, 17/228) although the difference was not statistically significant (p=0.090) and may have been due to confounding (for example, by clinical factors associated with treatment). However, the small number of cases precluded multivariable analysis.

4.4 Congenital abnormalities

Rates of congenital abnormalities were explored in infants born between 1990 and 2007. A total of 8576 infants were reported, including 95 who were stillborn and 288 twins or triplets. Information was available from both paediatric and obstetric sources for 79% (6631/8242) of infants, but the remainder were reported only through the obstetric (10%, 704/8242) or paediatric (11%, 907/8242) scheme. Information on congenital abnormality was available for 96.1% (8242/8576) of infants.

Infants with missing information on congenital abnormality

The 3.9% of infants with no information on congenital abnormality (n=334) were more likely than those with information available to be born before 2000 (44%, 146/334, versus 10%, p<0.001). They were therefore more likely than those with information reported to be born to untreated women (28%, 87/308, versus 6%, p<0.001), and to symptomatic women (16%, 45/275, versus 11%, p=0.004). They were also more likely to be preterm (25%, 80/323 versus 15%, p<0.001). Infants with missing information on congenital abnormalities were more likely to be stillborn (9.6%, 32/334, versus 0.8%, 63/8242, p<0.001); however, in general, delivery and perinatal information is poorly completed for stillbirths. Furthermore, in 40% of these stillbirths, it was unlikely that a congenital abnormality was present, either because the death was specifically reported as having no apparent cause (n=2) or because the death was attributed to another probable cause, including infection (n=2), pregnancy complications such as pre-eclampsia or placental abruption (n=6), twin-to-twin transfusion (n=2) or maternal liver failure (n=2). Overall, infants with missing information on congenital abnormality were no more likely than those with

information provided to have early ART exposure (15%, 44/289, versus 22%, p=0.478).

Maternal and pregnancy characteristics and ART

Among infants with information on congenital abnormalities reported (n=8242), ninety percent were born between 2000 and 2007 (Table 4.10). Three quarters were born to black African women, and 15% had mothers born in the UK or Ireland. Maternal region of birth and ethnic group were highly collinear: 82.5% (998/1210) of white women were born in the UK or Ireland, and 97.6% (6012/6162) of black African women were born in sub-Saharan Africa. Median maternal age at delivery was 30.0 years (interquartile range [IQR]: 26.3-33.8 years). Median gestational age was 38 weeks (IQR 37-39 weeks) and median birth weight was 3040 g (IQR 2700-3360 g). Median age at last follow up was six months (IQR: 3-15 months).

Information on timing of ART exposure was available for 92.6% (7633/8242) of infants; for those where information was missing, this was mostly (88%, 538/609) because reports were only obtained from paediatric respondents, who were not asked to provide this information. Less than a quarter of infants (22.4%, n=1708) had early *in utero* exposure, with the majority exposed later on (Table 4.10). Among first trimester regimens, most (52.9%) contained NNRTIs.

Congenital abnormalities

Altogether 232 infants out of 8242 were reported to have at least one congenital abnormality (2.8%, 95% CI: 2.5-3.2%), a quarter (59/232) of whom had only minor abnormalities (defined in Chapter 2, page 61, and shown in Table 4.13, page 141). The congenital abnormality rate excluding minor defects was 2.1% (95% CI: 1.8-

2.4%). All other abnormality rates shown here refer to major and minor abnormalities combined. Nineteen infants had more than one abnormality reported.

There were seven twin pregnancies where at least one twin had an abnormality, including one where both twins were affected (hydronephrosis). Abnormalities were reported in 11% (7/63) of stillborn infants. Nine infants with the following abnormalities were reported to have died neonatally: Down's syndrome, Trisomy 18, heart defects (n=3), achondroplasia, holoprosencephaly, dysmorphic features, intestine malrotation. Among the 194 live born infants with abnormalities, for whom HIV infection status was established, three (1.5%) were infected; one with a major heart abnormality, one with hydrocephalus, and one with congenital hip dislocation.

Congenital abnormality rates were marginally lower in infants born to black African mothers (2.6%) than in those born to white mothers (3.6%, p=0.051), and higher among infants whose mothers were symptomatic (4.1% versus 2.7%, p=0.029) (Table 4.10). Infants with abnormalities were more likely to be delivered prematurely (4.0% versus 2.6%, p=0.012) and to be of low birth weight. Abnormality rates were significantly higher in boys (3.3%) than in girls (2.2%, p=0.003), although if genital abnormalities (all of which were in boys) were excluded, the difference became non-significant (2.8%, 115/4101, versus 2.2%, 91/4079, p=0.098). There was also a statistically significant excess of limb abnormalities (almost all polydactyly) in boys (0.6%, 25/4123), compared with girls (0.2%, 7/4079, p=0.002).

Table 4.10 Rates and unadjusted odds ratios for congenital abnormalities by maternal, infant, and treatment characteristics

Characteristics (*n*=8242)	Total		Congenital abnormality				
	n	%	*n*	%	OR	(95% CI)	*p*-value
***Time period* (*n*=8242)**							
1990-1999	833	10.1	31	3.7	1.00		
2000-2007	7409	89.9	201	2.7	0.72	(0.49-1.06)	0.970
Maternal characteristics							
Ethnic origin (*n*=8171)							
White	1285	15.7	46	3.6	1.00		
Black African	6244	76.4	162	2.6	0.72	(0.51-1.00)	0.051
Black other	326	4.0	13	4.0	1.12	(0.60-2.10)	0.726
Other	316	3.9	10	3.2	0.88	(0.44-1.76)	0.719
Region of birth (*n*=8057)							
UK/ Ireland	1245	15.5	46	3.7	1.00		
Sub-Saharan Africa	6128	76.1	161	2.6	0.70	(0.50-0.98)	0.039
Elsewhere	684	8.5	22	3.2	0.87	(0.52-1.45)	0.586
Age at delivery (*n*=8184)							
<25 years	1471	18.0	40	2.7	1.00		
25-34 years	5154	63.0	147	2.9	1.05	(0.74-1.50)	0.786
≥ 35 years	1559	19.0	43	2.8	1.01	(0.66-1.57)	0.948
HIV exposure group (*n*=8242)							
Non-injecting drug use	7876	95.6	219	2.8	1.00		
Injecting drug use	366	4.4	13	3.6	1.29	(0.73-2.28)	0.384
Clinical status (*n*=7235)							
Asymptomatic	6451	89.2	174	2.7	1.00		
HIV-related symptoms/AIDS	784	10.8	32	4.1	1.54	(1.05-2.25)	0.029
Infant characteristics							
Sex (*n*=8202)							
Male	4123	50.3	137	3.3	1.00		
Female	4079	49.7	91	2.2	0.66	(0.51-0.87)	0.003
Gestational age (*n*=8056)							
≥37 weeks	6874	85.3	182	2.6	1.00		
<37 weeks	1182	14.7	47	4.0	1.52	(1.10-2.11)	0.012
Birth weight (*n*=7153)							
≥2500 g	6067	84.8	158	2.6	1.00		
<2500 g	1086	15.2	45	4.1	1.62	(1.15-2.27)	0.005
Treatment characteristics							
Timing of ART exposure(*n*=7633)							
Not treated in pregnancy	498	6.5	14	2.8	1.00		
Late (2nd/3rd trimester)	5427	71.1	147	2.7	0.96	(0.55-1.68)	0.893
Early (1st trimester)	1708	22.4	53	3.1	1.11	(0.61-2.01)	0.739
Treatment class in 1st trimester (*n*=1697)							
NRTI only	148	8.7	8	5.4	2.08	(0.92-4.72)	0.080
NNRTI	898	52.9	24	2.7	1.00		
PI	553	32.6	17	3.1	1.16	(0.61-2.17)	0.654
NNRTI & PI	98	5.8	3	3.1	1.15	(0.34-3.89)	0.822

There was no significant difference in the unadjusted abnormality rate by ART exposure, which was 2.8% in unexposed infants, 2.7% in those with late exposure, and 3.1% in those with early ART exposure (p=0.690) (Table 4.10). After adjusting for potential confounders (maternal ethnicity, age at delivery, injecting drug use and clinical status) neither late (AOR=0.96, 95% CI: 0.54-1.71, p=0.889) nor early ART exposure (AOR=1.01, 95% CI: 0.54-1.88, p=0.972) was significantly associated with congenital abnormality, compared with no exposure (n=7179) (Table 4.11). In adjusted analysis, abnormalities remained significantly lower in black African women compared with white women (AOR=0.66) and significantly higher in symptomatic women compared with asymptomatic women (AOR=1.51). Because of collinearity, analyses were not adjusted for maternal region of birth. If early exposure was instead compared with no early exposure, the difference in abnormality rates (3.1% versus 2.7%) remained non-significant: OR=1.14 (95% CI: 0.84-1.57, p=0.395), AOR=1.05 (95% CI: 0.75-1.47, p=0.776).

Class of ART was reported for 99.4% (1697/1708) of infants exposed in the first trimester. Because monotherapy and dual therapy were uncommon in early pregnancy (<3%, 48/1697), regimens were classified according to class of antiretrovirals rather than number of drugs. Class of regimen was not significantly associated with congenital abnormalities (p=0.363) (Table 4.10). Although the rate in infants exposed only to NRTIs was higher than for other drug classes, these infants were more likely to be reported in earlier years and therefore to be born to women who were young, white, symptomatic and/or had acquired HIV through injecting drug use (as shown in Chapter 3). In multivariable analysis (n=1679), PI-containing regimens were not associated with an increase in congenital abnormalities compared with NNRTI-containing regimens (AOR=1.09, 95% CI: 0.58-2.07, p=0.789), after adjusting for maternal ethnicity, age, injecting drug use and clinical status. Likewise,

in the same model there was no significantly increased risk associated with exposure to NRTI-containing regimens (AOR=1.94, 95% CI: 0.84-4.50, *p*=0.123) or to NNRTI- and PI-containing regimens (AOR=1.15, 95% CI: 0.34-3.92, *p*=0.823). Four infants in the PI group were also exposed to fusion inhibitors in the first trimester, but none had abnormalities reported.

Table 4.11 Unadjusted and adjusted odds ratios for congenital abnormalities

		Univariable (*n*=7179) *			Multivariable (*n*=7179)		
	n	**OR**	**(95% CI)**	***p*-value**	**AOR**	**(95% CI)**	***p*-value**
ART exposure and timing							
Not treated in pregnancy	447	1.00			1.00		
Late (2nd/3rd trimester)	5043	0.88	(0.50-1.53)	0.644	0.96	(0.54-1.71)	0.889
Early (1st trimester)	1689	1.00	(0.55-1.82)	0.995	1.01	(0.54-1.88)	0.972
Ethnic origin							
White	1105	1.00			1.00		
Black African	5471	0.67	(0.48-0.96)	0.028	0.66	(0.45-0.98)	0.039
Black other	318	1.08	(0.57-2.04)	0.815	1.12	(0.58-2.15)	0.735
Other	285	0.83	(0.40-1.72)	0.607	0.83	(0.39-1.75)	0.624
Age at delivery							
<25 years	1264	1.00			1.00		
25-34 years	4516	1.14	(0.78-1.68)	0.504	1.19	(0.80-1.76)	0.392
≥ 35 years	1399	1.07	(0.67-1.71)	0.779	1.08	(0.66-1.75)	0.758
HIV exposure group							
Other risk	6891	1.00			1.00		
Injecting drug use	288	1.36	(0.73-2.53)	0.326	0.96	(0.48-1.94)	0.912
Clinical status							
Asymptomatic	6404	1.00			1.00		
HIV-related symptoms/AIDS	775	1.54	(1.05-2.27)	0.027	1.51	(1.02-2.25)	0.041

* Univariable analysis for infants included in the multivariable model.

Efavirenz and didanosine

A total of 220 infants were exposed to efavirenz, 205 (93.2%) in early pregnancy; of those exposed early, 2.4% (5/205) had abnormalities reported (undescended testes [*n*=2], hip dislocation [*n*=2], hypertrophic pyloric stenosis). This rate did not differ significantly from the rate in infants with first trimester ART exposures other than efavirenz (3.2%, 48/1503, *p*=0.672). There were 284 exposures to didanosine, 174 (61.3%) in the first trimester; of those infants with early didanosine exposure, 3.4% (6/174) had abnormalities reported (Down's syndrome, heart defect [*n*=2], hydronephrosis, jejunal atresia, foot abnormality); again, this rate did not differ significantly from the rate for other first trimester ART exposures (3.1%, 47/1534, *p*=0.816). However, there was sufficient power (>80%) to detect only about a 2.5-fold increase in risk associated with didanosine or efavirenz exposure. There were no abnormalities reported in infants exposed to efavirenz (*n*=15) or didanosine (*n*=110) later in pregnancy.

Type of abnormalities

No category of abnormality was significantly associated with first trimester exposure, although power to detect an association was limited due to small numbers (Table 4.12). Of the 12 cases of hypospadias, all were in infants exposed to zidovudine-containing regimens (0.18%, 12/6711); however, the rate did not differ significantly from the rate in infants exposed to zidovudine-sparing regimens (0%, 0/792, *p*=0.262). Timing of ART was reported for 11 of these infants: two had early exposure (2/1708, 0.12%; or 2/856 boys, 0.23%), and nine late (9/5427, 0.17%; 9/2693 boys, 0.33%), with no statistically significant difference between the two groups (*p*=1.00). Individual abnormalities by timing of treatment are shown in Table 4.13. There was no clear excess in any particular abnormality in infants with early

exposure, except for renal dilatation, which was reported in 0.18% (3/1708) of infants exposed to ART in the first trimester, but only 0.02% (1/5929) of unexposed infants, a difference which was just statistically significant (Fisher's exact test, p=0.037). However, given the number of different abnormalities (and consequently the number of statistical tests carried out in order to compare rates in all the different groups), this finding should be treated with caution, particularly since it was based on only four infants with the abnormality.

Table 4.12 Reported category of congenital abnormality by timing of ART exposure

	Total		Total with timing information*		Timing of ART exposure						
					None		Late (2nd/3rd trimester)		Early (1st trimester)		
Type of abnormality	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	***p* value ****
Nervous system	17	0.21	16	0.21	1	0.20	11	0.20	4	0.23	0.767
Ear, face, neck & eye	5	0.06	4	0.05	0	0.00	3	0.06	1	0.06	1.000
Heart & circulatory	30	0.36	25	0.33	0	0.00	16	0.29	9	0.53	0.144
Respiratory system	4	0.05	3	0.04	1	0.20	2	0.04	0	0.00	1.000
Cleft palate/lip	7	0.08	7	0.09	1	0.20	5	0.09	1	0.06	1.000
Digestive system	18	0.22	18	0.24	1	0.20	11	0.20	6	0.35	0.262
Genital organs	22	0.27	19	0.25	3	0.60	11	0.20	5	0.29	0.594
Urinary system	20	0.24	19	0.25	1	0.20	11	0.20	7	0.41	0.163
Musculoskeletal	40	0.49	38	0.50	2	0.40	27	0.50	9	0.53	0.846
Limbs	32	0.39	30	0.39	3	0.60	23	0.42	4	0.23	0.279
Integument	11	0.13	10	0.13	0	0.00	7	0.13	3	0.18	0.474
Chromosomal	21	0.25	20	0.26	1	0.20	16	0.29	3	0.18	0.594
Other & unspecified anomalies	2	0.02	2	0.03	0	0.00	1	0.02	1	0.06	0.397
Type not specified	3	0.04	3	0.04	0	0.00	3	0.06	0	0.00	1.000
Total congenital abnormalities	232	2.81	214	2.80	14	2.81	147	2.71	53	3.10	
Total infants	8242		7633		498		5427		1708		

* Excludes 18 infants with abnormalities for whom information on timing of treatment was not available.
** Fisher's exact test for comparison of first trimester exposure with late or no exposure.

Table 4.13 Reported congenital abnormalities (grouped by category) by timing of ART exposure

Abnormality by WHO category	Early ART exposure: No	Yes
Total infants	5929	1708
Total abnormalities	161	53
Nervous system		
Hydrocephalus	5	1
Sub-ependymal cysts *	0	1
Spina bifida	2	2
Cerebral atrophy	1	0
Absent corpus callosum	1	0
Holoprosencephaly	1	0
Microcephaly	1	0
Dandy-Walker syndrome	1	0
Eye, ear, face, neck		
Malformed ear *	1	0
Ptosis of eye	1	0
Minor mouth abnormalities *	0	1
Duane's syndrome	1	0
Heart & circulatory		
Heart defects (unspecified)	3	1
Pulmonary stenosis	3	0
Heart (Ebstein's anomaly)	0	1
Heart (patent ductis arteriosus)	3	2
Heart (septal defects)	4	4
Stenosis of aortic valve	1	0
Heart (Tetralogy of Fallot)	1	0
Heart (truncus arteriosus)	0	1
Heart (cardiomyopathy)	1	0
Respiratory		
Lung abnormality	1	1
Stridor (laryngeal)	1	1
Cyst adenomatoid malformation	1	1
Cleft palate/lip		
Cleft palate and/or hare lip	6	1
Digestive		
Biliary atresia	1	0
Bowel obstruction/abnormalities	5	2
Jejunal atresia	2	1
Anal polyp	1	0
Macroglossia *	1	0
Duodenal atresia	0	1
Hypertrophic pyloric stenosis	0	1
Intestine malrotation	1	1
Imperforate anus	1	0

Abnormality by WHO category	Early ART exposure: No	Yes
Genital organs		
Hypospadias	9	2
Undescended testes *	5	2
Ambiguous genitalia	0	1
Urinary		
Hydronephrosis	7	3
Urethral/bladder problem	1	0
Renal dilatation	1	3
Dysplastic kidney	3	1
Musculoskeletal		
Skeletal problems/hemivertebrae	1	1
Exomphalos	0	1
Talipes	17	3
Spinal hairy patch *	0	1
Abnormalities of feet *	1	1
Hip dislocation	4	2
Cleidocranial dysostosis	1	0
Caffeys syndrome	1	0
Diaphragmatic hernia	1	0
Achondroplasia	1	0
Osteodystrophy	1	0
Gastroschisis	1	0
Limbs		
Extra digits *	26	3
Larsen syndrome	0	1
Integument		
Accessory nipples *	2	0
Strawberry naevus *	4	0
Skin tag *	1	1
Birthmark *	0	2
Chromosomal		
Down's syndrome	13	2
Trisomy 18	3	0
Chromosomal anomaly	1	0
Turner's syndrome	0	1
Other & unspecified		
Prader-Willi syndrome	0	1
Beckwith-Wiedemann syndrome	1	0
Type not specified		
Unspecified congenital anomaly	2	2
Dysmorphic features	1	1

* Abnormalities classified as minor.
N.B. Excludes 18 congenital abnormalities (6 minor) in infants with missing information on timing of maternal ART.

Abnormalities in terminated pregnancies

In addition to abnormalities in live born and stillborn infants, 21 congenital abnormalities were reported in 549 terminated pregnancies (1990-2007); these were anencephaly (*n*=4), Down's syndrome (*n*=5), other chromosomal anomaly (*n*=3), exomphalos, enlarged cerebral ventricles, cleft lip/palate, hydronephrosis, bowel abnormality, heart defect, spina bifida, achondroplasia, and renal agenesis. These 21 terminations were carried out between 12 and 30 weeks gestation, and only five (three Down's syndrome) were in women who were on treatment (HAART) in early pregnancy. The overall abnormality rate including these 21 terminations was 3.1% (253/8263, 95% CI: 2.7-3.5).

4.5 Key Points

- The stillbirth rate was 10.9 per 1000 births (95% CI: 8.8-13.4 per 1000 births), and was three times higher in women on HAART (11 per 1000) than in women on monotherapy (3 per 1000) after adjusting for other risk factors.
- Pregnancy complications (other than stillbirth and prematurity) were reported in 7.7% (285/3852) of pregnancies, and were more common in older women and those with HIV-related symptoms or low CD4 count (<200 cells/µl), as well as in multiple pregnancies.
- Pre-eclampsia was reported in 2% of pregnancies, and was significantly associated with type and timing of HAART: a lower rate of pre-eclampsia (1.6%) was reported in women who initiated PI-based HAART in pregnancy, compared with those who were on HAART at conception (2.9%) or those who initiated non-PI-based HAART in pregnancy (2.8%).
- Among women starting HAART in pregnancy, later initiation of HAART was associated with a 6% decrease in pre-eclampsia for each gestation week without HAART.
- The congenital abnormality rate in 8242 infants born in the UK or Ireland to HIV-infected women (1990-2007) was 2.8% (95% CI: 2.5-3.2%).
- Congenital abnormality rates were not associated with timing of *in utero* ART exposure, nor with class of first trimester ART exposure.
- Despite reports of increased abnormality rates associated with early efavirenz or didanosine exposure, no such association was detected in this population, nor was any association detected between early ART exposure and rates of hypospadias.

Chapter 5 Antiretroviral therapy and premature delivery

Evidence suggesting an increased risk of premature, or preterm, delivery associated with highly active antiretroviral therapy (HAART) in pregnancy has been accumulating in recent years (Boer *et al.*, 2007; Cotter *et al.*, 2006; European Collaborative Study, 2004a). Studies in the United States (US), however, have produced conflicting results, with some finding no association between treatment and preterm delivery (Tuomala *et al.*, 2002; Tuomala *et al.*, 2005), and others suggesting a possible association with protease inhibitor (PI)-containing HAART (Cotter *et al.*, 2006; Schulte *et al.*, 2007). Reasons for these conflicting findings have remained unclear, although several methodological issues have been highlighted including differences in populations, type of data collected and analytical approach, as well as the inability to control for other known risk factors for prematurity in some studies (Tuomala & Yawetz, 2006).

The first part of this chapter addresses the association between antiretroviral therapy (ART) and premature delivery in the UK and Ireland, using data from the National Study of HIV in Pregnancy and Childhood (NSHPC) (related publication shown in Appendix 2, page 357) (Townsend *et al.*, 2007). In the second part of the chapter, data from the NSHPC are compared with data from the European Collaborative Study (ECS), and the Pediatric Spectrum of HIV Disease project (PSD) in the US. Differences between the studies are investigated, including the role of methodology, population characteristics and analytical approach in explaining any variation between studies in the observed association between ART and prematurity.

5.1 Methods specific to this chapter

Because multiple pregnancy is a risk factor for prematurity (Slattery & Morrison, 2002), all analyses in this chapter were restricted to singleton births. The association between ART and gestational age was explored using a categorical variable for prematurity, defined as delivery at <37 weeks gestation (Goldenberg *et al.*, 2008). Because elective caesarean section deliveries for prevention of mother-to-child transmission are usually scheduled at 38 weeks gestation (BHIVA, 2005a; BHIVA/CHIVA, 2008; Coll *et al.*, 2002; Perinatal HIV Guidelines Working Group, 2005), categorising gestational age as <37 weeks avoided the methodological complication of a change over time in the proportion of elective caesarean section deliveries.

Odds ratios (ORs) were adjusted for known risk factors for prematurity on which information was available; these included maternal injecting drug use (IDU), clinical status and ethnic group (Aveyard *et al.*, 2002; Institute of Medicine, 2006; Patel *et al.*, 2004; Schulte *et al.*, 2007; Slattery & Morrison, 2002). A U-shaped association between maternal age and premature delivery has also been reported, with younger (<20 years of age) and older mothers (>35 years of age) being at increased risk of preterm delivery (Slattery & Morrison, 2002); it was therefore appropriate to include maternal age as a categorical variable.

NSHPC analysis

The NSHPC analysis was based on all singleton live births and stillbirths delivered between 1990 and 2005, in women diagnosed as HIV-infected before delivery and reported through the obstetric scheme by March 2006. In most analyses, monotherapy and dual therapy were combined, due to the relatively small number of

pregnancies in women on dual therapy (*n*=157, 3%). Timing of initiation of treatment was classified as before pregnancy or in the first trimester (up to 12 completed weeks gestation); second trimester (13-26 completed weeks gestation); or third trimester (after 26 weeks gestation). Year of delivery was grouped according to availability of ART: 1990-1993 (pre-ART); 1994-1999 (monotherapy and introduction of HAART); 2000 onwards (HAART and selective monotherapy for women with low viral load). Maternal clinical status was defined as any HIV-related symptoms or AIDS reported at any time in pregnancy (Centers for Disease Control and Prevention, 1992).

In order to assess differences in birth weight between groups independently of gestational age, a *z*-score (standard deviation from the population mean) was calculated for each birth weight according to gestational age and gender, using British 1990 population standards (Cole, Freeman, & Preece, 1998). *Z*-scores were obtained using LMSgrowth, a Microsoft Excel add-in available at www.healthforallchildren.co.uk (Accessed 26 January 2009), which employs the LMS method (Cole & Green, 1992). This method summarises growth reference data with three curves representing the median (M), the coefficient of variation (S) and the skewness (L) as they change with age.

To allow for repeat pregnancies in the same woman, generalized linear mixed effects were used to fit logistic regression models accounting for random effects attributed to the mother (command '`xtlogit`' in Stata) (Rabe-Hesketh, Skrondal, & Pickles, 2002). Only random effects on the intercept of the linear predictor were considered; these act as a subject-specific risk baseline corresponding to unobserved, mother-specific variables. Due to improvements in the estimation criteria for '`xtlogit`'

between Stata versions 9.0 and 10.0, results presented here differ slightly from published findings (Townsend *et al.*, 2007).

5.2 ART and prematurity in the NSHPC

The association between ART and prematurity was first explored in pregnancies reported to the NSHPC. Between 1990 and 2005, a total of 5009 singleton births were reported, with an overall prematurity rate of 13.3% (667/5009). Seventy pregnancies (1.3%) had inadequate information on type or timing of ART (before or during pregnancy), and were excluded; these did not differ from those for which treatment information was available in terms of prematurity, but a higher proportion occurred before 2000 (34% versus 17%, $p<0.001$). Because of the changes over time in demographic characteristics (described in Chapter 3), white women (27% versus 17%, $p=0.023$) and women with IDU-acquired infection (12% versus 5%, $p<0.001$) were over-represented in this group.

Pregnancies in treated and untreated women

There were clear baseline differences between ART-treated and untreated women, and between women on monotherapy or dual therapy (mono/dual therapy) and those on HAART (Table 5.1), reflecting concurrent changes in the characteristics of HIV-infected women over time along with trends in ART use in pregnancy (Chapter 3). There were also differences in availability of test results between the three groups; for example, CD4 count was available for 88.0% (2977/3384) of women on HAART and 76.2% (808/1061) of those on mono/dual therapy, but for only 41.3% (204/494) of untreated women.

Pregnancies in untreated women

There were 494 pregnancies in untreated women. As these were more likely to have occurred in the earlier years than pregnancies in treated women, they were more likely to be in white women (33.7%, 164/486, versus 14.6%, 650/4443, $p<0.001$) and in women with IDU-acquired infection (20.0%, 99/494, versus 3.4%, 149/4449).

The prematurity rate in untreated women was 15.6% (77/494) and increased over time, from 11.0% (20/181) in 1990-1993, to 16.7% (26/156) in 1994-1999 and 19.7% (31/157) in 2000-2005 ($p=0.004$). Two of the main reasons for being untreated in the latter period (when over 95% of women received ART in pregnancy) were late diagnosis and premature delivery; in 2000-2005, 22.3% (35/157) of untreated women were diagnosed with HIV within two weeks of delivery, compared with only 1.0% (41/3950) of treated women ($p<0.001$). Furthermore, among women who delivered prematurely in 2000-2005, diagnosis was within two weeks of delivery in 29% (9/31) of untreated women but only 2% (9/522) of treated women ($p<0.001$). Because of biases introduced by these changes over time, these pregnancies in untreated women were not an appropriate comparison group for those in women on HAART.

Pregnancies in ART-treated women

Most of the 4445 pregnancies with ART exposure were in black African women, and few were in women with IDU-acquired infection (Table 5.1). Median maternal age at delivery was 29.7 years (range: 14.8-47.4 years, interquartile range [IQR]: 26.2-33.6 years).

Table 5.1 Demographic characteristics by category of antiretroviral therapy received in pregnancy

Maternal and pregnancy characteristics (*n* =4939)	Untreated (*n* =494)		Mono/dual therapy (*n* =1061)		HAART (*n* =3384)		HAART vs. mono/dual
	n	%	*n*	%	*n*	%	χ^2 *p* -value
Ethnic origin (n=4929)							
White	164	(33.7)	211	(19.9)	439	(13.0)	
Black African	303	(62.3)	763	(72.0)	2647	(78.2)	
Other	19	(3.9)	86	(8.1)	297	(8.8)	<0.001
Age at delivery (n=4937)							
<25 years	124	(25.2)	239	(22.5)	572	(16.9)	
25-34 years	334	(67.7)	681	(64.2)	2161	(63.9)	
≥35 years	35	(7.1)	140	(13.2)	651	(19.2)	<0.001
Exposure category (n=4939)							
Injecting drug use	99	(20.0)	68	(6.4)	81	(2.4)	
Other*	395	(80.0)	993	(93.6)	3303	(97.6)	<0.001
Timing of diagnosis (n=4939)							
Before pregnancy	253	(51.2)	397	(37.4)	1606	(47.5)	
During pregnancy	241	(48.8)	664	(62.6)	1778	(52.5)	<0.001
Parity (n=4352)							
Nulliparous	69	(22.0)	318	(33.8)	1082	(34.9)	
Parous	244	(78.0)	624	(66.2)	2015	(65.1)	0.505
Clinical status (n=4895)							
Asymptomatic	418	(86.2)	962	(91.5)	2919	(86.9)	
HIV symptoms or AIDS	67	(13.8)	89	(8.5)	440	(13.1)	<0.001
CD4 count (n=3989)							
≥500 cells/µl	63	(30.9)	387	(47.9)	895	(30.1)	
200-499 cells/µl	110	(53.9)	372	(46.0)	1628	(54.7)	
<200 cells/µl	31	(15.2)	49	(6.1)	454	(15.3)	<0.001
HIV RNA viral load (n=3257)							
<50 copies/ml	12	(11.2)	163	(30.6)	1772	(67.7)	
51-999 copies/ml **	22	(20.6)	213	(40.0)	625	(23.9)	
1000-9999 copies/ml	31	(29.0)	133	(25.0)	133	(5.1)	
>10,000 copies/ml	42	(39.3)	23	(4.3)	88	(3.4)	<0.001
Mode of delivery (n=4676)							
Elective caesarean section	83	(29.3)	702	(68.1)	1996	(59.4)	
Emergency caesarean section	55	(19.4)	144	(14.0)	689	(20.5)	
Vaginal	145	(51.3)	185	(17.9)	677	(20.1)	<0.001
Year of delivery (n=4939)							
1990-93	181	(36.6)	14	(1.3)	0		
1994-99	156	(31.6)	317	(29.9)	164	(4.8)	
2000-05	157	(31.8)	730	(68.8)	3220	(95.2)	<0.001

N.B. Excludes 70 pregnancies with missing information on type or timing of ART.
* Includes exposure in area of high HIV prevalence, blood transfusion, and other/unknown risk.
** Includes viral loads reported as '<200 copies/ml' or '<400 copies/ml' (*n*=85; 1 untreated, 21 mono/dual therapy, 63 HAART).

Most deliveries were by elective caesarean section (Table 5.1), and median gestational age was 38 weeks (IQR: 38-39 weeks). Compared with HAART, mono/dual therapy was associated with being younger, white, and acquiring HIV through IDU (Table 5.1); this again related to issues of timing, with monotherapy having been available earlier than HAART (Chapter 3, Figure 3.3, page 83). Mono/dual therapy was also associated with higher viral load, probably because HAART is more effective than monotherapy or dual therapy at reducing viral load. However, HAART was associated with lower CD4 cell count, possibly because women with low baseline CD4 count would have been put on HAART if it was available.

Most women took HAART in pregnancy; HAART more frequently included a non-nucleoside reverse transcriptase inhibitor (NNRTI) than a PI (Table 5.2). Over a quarter of women on HAART were on treatment early in pregnancy (Table 5.2), whereas most women taking mono/dual therapy started later (94.9%, 1007/1061). Of the 914 women on HAART early, 41 started it during the first trimester, at a median of 11 weeks (IQR: 7-12 weeks). Among those starting treatment later in pregnancy, timing of ART initiation was available for 92.9% (3477/3744) of pregnancies: women on mono/dual therapy started treatment slightly but significantly later than women on HAART (median gestation, 28.1 weeks versus 26.2 weeks, $p<0.001$). However, the proportion of pregnancies in which treatment was initiated within the last two weeks of pregnancy did not differ by type of ART (HAART: 4.7%, 113/2385, mono/dual therapy: 4.5%, 43/951, $p=0.789$), even among women who delivered prematurely (HAART, 12.0%, 38/317; mono/dual, 11.0%, 10/91, $p=0.794$).

Table 5.2 Use of antiretroviral therapy

	Total		Premature	
Antiretroviral therapy (*n*=4445)	*n*	%	*n*	%
Type of ART (n=4445)				
Monotherapy	904	(20.3)	97	(10.7)
Dual therapy *	157	(3.5)	10	(6.4)
HAART	3384	(76.1)	476	(14.1)
Type of HAART (n=3384)				
- with NRTIs only	69	(2.0)	6	(8.7)
- with NNRTI(s)	1831	(54.1)	261	(14.3)
- with PI(s)	1256	(37.1)	169	(13.5)
- with PI(s) & NNRTI(s)	228	(6.7)	40	(17.5)
Timing of HAART (n=3299)*				
Before pregnancy / first trimester ***	914	(27.7)	150	(16.4)
Second trimester	1287	(39.0)	188	(14.6)
Third trimester	1098	(33.3)	129	(11.7)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

* Of the 157 dual therapy regimens, three included one PI, and one included two PIs.
** Excludes 85 pregnancies in which HAART was started during pregnancy, but no dates were given.
*** Includes 41 pregnancies in which HAART was initiated during the first trimester.

Prematurity rates and risk factors

The overall prematurity rate in ART-treated pregnancies was 13.1% (583/4445, 95% CI: 12.1-14.2%); 51.8% (302/583) of premature deliveries were at <35 weeks, including 23.3% (136/583) at <32 weeks. There was no trend in the rate of premature delivery (<37 weeks) over time (p=0.759). Prematurity was not significantly associated with maternal age (Table 5.3), even when age was broken down into smaller age groups: rates were 11.3% (17/150) in women under 20 years of age, and 13.7% (14/102) in those over 39 years of age, compared with 12.4% (186/1496) in women aged 25-29 years (p=0.696 and p=0.703 respectively). There was no association between prematurity and maternal ethnic group, but acquisition of HIV through IDU, and HIV-related symptoms in pregnancy were associated with a significantly increased risk of prematurity (Table 5.3).

The prematurity rate was 10.7% in pregnancies with monotherapy exposure, 6.4% in those with dual therapy exposure and 14.1% with HAART exposure (Table 5.2). As there were only a small number of women on dual therapy, and the prematurity rate was not significantly different from those on monotherapy (p=0.094), these two groups were combined; the prematurity rate in the combined group was 10.1% (107/1061) (Table 5.3).

HAART was associated with a significantly increased risk of prematurity compared with mono/dual therapy in univariable analysis (OR=1.46) (Table 5.3); including a random effect term to control for repeat pregnancies led to a slight increase in the OR, to 1.61. ORs were then adjusted for known risk factors, on which information was available (clinical status, IDU-acquired infection, ethnic group and maternal age); ethnic group and maternal age were included despite not being significant in

univariable analysis, to enable comparison with other studies (e.g. European Collaborative Study, 2004a; Schulte *et al*., 2007). In multivariable analyses, the association between HAART and prematurity remained significant (AOR=1.63, p=0.001), and all ORs were very similar in the unadjusted and adjusted models (Table 5.3). There were no significant interactions between ART and any of the covariates included in the models.

Table 5.3 Rates, unadjusted and adjusted odds ratios for premature delivery

	n	% premature	Univariable OR (95% CI)	*p* -value	Univariable - adjusted for repeat pregnancies OR (95% CI)	*p* -value	Multivariable - adjusted for repeat pregnancies (*n* =4407) AOR (95% CI)	*p* -value
Antiretroviral therapy								
Mono/dual therapy	1061	10.1	1.00		1.00		1.00	
HAART	3384	14.1	1.46 (1.17-1.82)	0.001	1.61 (1.21-2.15)	0.001	1.63 (1.22-2.19)	0.001
Ethnic origin								
White	650	14.2	1.00		1.00			
Black African	3410	12.7	0.97 (0.78-1.21)	0.765	0.98 (0.74-1.30)	0.882	1.11 (0.76-1.62)	0.590
Other	383	15.1	1.20 (0.86-1.68)	0.273	1.21 (0.79-1.86)	0.377	1.39 (0.83-2.32)	0.211
Maternal age at delivery								
<25 years	811	12.8	1.00		1.00			
25-34 years	2842	12.9	0.97 (0.78-1.20)	0.794	0.96 (0.74-1.26)	0.792	0.94 (0.69-1.29)	0.715
≥35 years	791	14.0	1.10 (0.84-1.45)	0.468	1.13 (0.81-1.59)	0.470	1.03 (0.70-1.50)	0.896
Source of infection								
Other/no known risk	4296	12.8	1.00		1.00			
Injecting drug use	149	22.1	1.64 (1.19-2.25)	0.002	1.88 (1.23-2.88)	0.004	2.78 (1.44-5.38)	0.002
Clinical status								
Asymptomatic	3881	12.4	1.00		1.00			
HIV-related symptoms or AIDS	529	18.5	1.58 (1.26-1.98)	<0.001	1.76 (1.31-2.36)	<0.001	1.75 (1.26-2.43)	0.001

N.B. All rates and odds ratios are in ART-treated women only. Adjustment for repeat pregnancies was by inclusion of a random effect term.

CD4 count and viral load

CD4 count was reported for 85.3% (3792/4445) of pregnancies, and was measured at a median of 29 days before delivery (IQR: 14-56 days). Median CD4 count was 400 cells/µl (IQR: 270-560 cells/µl). Viral load was reported for 70.9% of pregnancies (3150/4445), and was measured at a median of 21 days before delivery (IQR: 8-36 days). Median viral load was <50 copies/ml (IQR: <50-158 copies/ml) overall, and 300 copies/ml (IQR 103-1600 copies/ml) among the 38.6% (1215/3150) of women with detectable viral load (≥50 copies/ml).

CD4 count and viral load were significantly associated with prematurity rates, which tended to be increased in women with low CD4 counts or high viral loads (Table 5.4). The prematurity rate in pregnancies with missing CD4 count was higher than in those with CD4 reported (17% versus 12% respectively, $p<0.001$), and similarly for viral load (16% versus 13% respectively, $p=0.015$), probably reflecting lack of opportunity for testing women in premature labour.

Table 5.4 CD4 count, viral load and prematurity: rates and unadjusted odds ratios

	Total	Premature		Univariable	
	n	***n***	**%**	**OR (95% CI)**	***p*-value**
CD4 cell count (cells/µl)					
≥500	1282	130	10.1	1.00	
200-500	2000	267	13.4	1.53 (1.10-2.13)	0.012
<200	503	80	15.9	2.14 (1.34-3.41)	0.001
Missing	1295	220	17.0		
Viral load (copies/ml)					
<50	1935	199	10.3	1.00	
51-999 *	838	112	13.4	1.51 (1.04-2.17)	0.028
1000-9999	266	41	15.4	1.91 (1.10-3.31)	0.022
>10,000	111	11	9.9	0.98 (0.40-2.41)	0.965
Missing	660	106	16.1		

* Includes 84 cases with viral load reported as '<200 copies/ml' or '<400 copies/ml'.

Initially, separate models including either CD4 count or viral load were developed, to avoid over-adjusting for factors that were potentially on the same causal pathway. Although the suggested effect of HAART on prematurity is mediated through the cytokine environment (not through viral load and CD4 count), the possible confounding effects of viral load and CD4 cell count may be on the same causal pathway: HAART reduces viral load, leading to an increase in CD4 cell counts, which may reduce the risk of preterm delivery (see Figure 7.1, page 278). Restricting the logistic regression model to pregnancies where viral load was reported led to a reduction in the AOR for the association between HAART and prematurity, and loss of statistical significance (AOR=1.46, p=0.113), partly due to a reduction in the number of births (from 4407 to 3136). However, after adjusting for viral load, HAART was associated with a significantly increased risk of prematurity (AOR=1.92). Including CD4 count in the model reduced the AOR slightly (from 1.64 to 1.54), but the association remained significant (p=0.027; Table 5.5). Both viral load and CD4 count were independently associated with prematurity in separate models (Table 5.5). However, when they were included in the same model (n=2994), CD4 count was no longer significant (likelihood ratio test [LRT], p=0.257). The association between HAART and prematurity remained significant in this model, which included ethnic group, maternal age, IDU-acquired infection, clinical status, CD4 count, viral load and repeat pregnancies (AOR=1.88, 95% CI: 1.10-3.22, p=0.021).

Table 5.5 Adjusted odds ratios for premature delivery, including viral load or CD4 count

	Subset with CD4 reported (*n* =3761)		Adjusting for CD4 count (*n* =3761)		Subset with viral load reported (*n* =3136)		Adjusting for viral load (*n* =3136)	
	AOR (95% CI)	*p* -value	AOR (95% CI)	*p* -value	AOR (95% CI)	*p* -value	AOR (95% CI)	*p* -value
Antiretroviral therapy								
Mono/dual therapy	1.00		1.00		1.00		1.00	
HAART	1.64 (1.12-2.41)	0.011	1.54 (1.05-2.25)	0.027	1.46 (0.91-2.33)	0.113	1.92 (1.17-3.15)	0.010
Ethnic origin								
White	1.00		1.00		1.00		1.00	
Black African	1.11 (0.68-1.79)	0.677	1.02 (0.63-1.66)	0.929	0.94 (0.55-1.59)	0.814	0.92 (0.55-1.55)	0.760
Other	1.49 (0.78-2.83)	0.228	1.43 (0.75-2.71)	0.274	1.40 (0.68-2.86)	0.360	1.34 (0.67-2.69)	0.413
Maternal age at delivery (years)								
<25	1.00		1.00		1.00		1.00	
25-34	0.87 (0.59-1.28)	0.474	0.84 (0.57-1.24)	0.382	0.95 (0.61-1.48)	0.810	0.98 (0.64-1.53)	0.946
≥35	1.02 (0.63-1.64)	0.939	0.97 (0.60-1.56)	0.899	1.22 (0.71-2.09)	0.468	1.31 (0.77-2.23)	0.314
Source of infection								
Other/no known risk	1.00		1.00		1.00		1.00	
Injecting drug use	2.68 (1.12-6.44)	0.027	2.52 (1.05-6.01)	0.038	2.79 (0.96-8.11)	0.059	2.75 (0.97-7.82)	0.058
Clinical status								
Asymptomatic	1.00		1.00		1.00		1.00	
HIV-related symptoms or AIDS	1.94 (1.28-2.93)	0.002	1.78 (1.18-2.70)	0.006	2.20 (1.36-3.54)	0.001	2.18 (1.36-3.51)	0.001
CD4 cell count (cells/μl)								
≥500	NA		1.00		NA		NA	
200-500	NA		1.45 (1.04-2.02)	0.028	NA		NA	
<200	NA		1.81 (1.13-2.89)	0.014	NA		NA	
Viral load (copies/ml)								
<50	NA		NA		NA		1.00	
51-999	NA		NA		NA		1.71 (1.18-2.50)	0.005
1000-9999	NA		NA		NA		2.60 (1.44-4.71)	0.002
>10,000	NA		NA		NA		1.07 (0.44-2.62)	0.878

NA, not applicable. * Includes viral loads reported as <200 copies/ml or <400 copies/ml. All AORs adjusted for ART, ethnic group, maternal age, IDU-acquired infection, clinical status, and repeat pregnancies.

Severe prematurity

The association between HAART and prematurity was more pronounced for delivery at <35 weeks and <32 weeks (AOR=2.78 and 2.70, respectively), than at <37 weeks gestation (AOR=1.63) (Table 5.6).

Type of HAART

Among 3384 HAART-exposed pregnancies, premature delivery occurred in 8.7% of those with exposure to NRTIs only, 14.3% with NNRTI exposure, 13.5% with PI exposure, and 17.5% with both PI and NNRTI exposure (χ^2=4.37, df=3, *p*=0.224) (Table 5.2). After adjusting for clinical status, IDU, ethnic group and maternal age, PI-based HAART was not associated with a significantly increased risk of prematurity compared with NNRTI-based HAART (AOR=0.85, 95% CI: 0.63-1.15, *p*=0.302), nor were regimens which included both PIs and NNRTIs (AOR=1.14, 95% CI: 0.66-1.95, *p*=0.644) or those consisting only of NRTIs (AOR=0.41, 95% CI: 0.13-1.33, *p*=0.138). However, statistical power to detect a significant difference between these subgroups was limited.

Table 5.6 Odds ratios for delivery at <37 weeks, <35 weeks and <32 weeks gestation in women on HAART compared with mono/dual therapy

			Univariable (*n*=4445)		Multivariable (*n*=4407)	
Timing of delivery	***n***	**% pre-mature**	**OR (95% CI)**	***p*-value**	**AOR (95% CI)**	***p*-value**
<37 weeks						
Mono/dual	1061	10.1	1.00		1.00	
HAART	3384	14.1	1.61 (1.21-2.15)	0.001	1.63 (1.22-2.19)	0.001
<35 weeks						
Mono/dual	1061	3.6	1.00		1.00	
HAART	3384	7.8	2.70 (1.72-4.25)	<0.001	2.78 (1.74-4.44)	<0.001
<32 weeks						
Mono/dual	1061	1.4	1.00		1.00	
HAART	3384	3.6	2.74 (1.51-4.95)	0.001	2.70 (1.48-4.92)	0.001

N.B. Univariable analyses were adjusted for repeat pregnancies only; multivariable analysis was adjusted for IDU-acquired infection, ethnic group, maternal age, clinical status, and repeat pregnancies.

Timing of initation of ART

Among women starting HAART in pregnancy, later initiation of therapy was associated with a 7% reduction in the risk of prematurity for each additional week of gestation without treatment, after adjusting for clinical status, IDU-acquired infection, ethnic group and maternal age (OR=0.93 per week of gestation, 95% CI: 0.90-0.97, $p<0.001$, $n=2426$; AOR=0.94, 95% CI: 0.91-0.98, $p=0.001$, $n=2412$). However, lower prematurity rates would naturally be expected in women who started treatment in the later stages of pregnancy, because this group would exclude women who were due to start ART later, but delivered before initiating treatment. Because this effect could potentially lead to an over-estimate of the association between prematurity and duration of HAART, the analysis was limited to 1328 women who initiated treatment before the end of the second trimester (i.e. by 26 completed weeks gestation). Later exposure to HAART was associated with a 10% reduction in prematurity per gestation week without HAART (OR=0.89 per week gestation, 95% CI: 0.83-0.96, $p=0.003$; AOR=0.91, 95% CI: 0.84-0.97, $p=0.007$; $n=1322$). Prematurity rates by grouped gestation week at initiation are shown in Table 5.7; the prematurity rate in women who started HAART before pregnancy (16.2%, 148/913) was not significantly higher than the rate in those who started HAART in the first 19 weeks of pregnancy (17.5%, 66/377, $\chi^2=0.324$, df=1, $p=0.578$), but numbers were small.

Table 5.7 Odds ratios and adjusted odds ratios for premature delivery by timing of initiation of HAART

Gestation week at initiation of HAART	*n*	% pre-mature	OR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
≥32	333	9.3	*			
27-31	765	12.8	*			
20-26	1011	13.8	1.00		1.00	
13-19	276	17.4	1.46 (0.86-2.50)	0.163	1.47 (0.82-2.64)	0.192
0-12	41	22.0	2.38 (0.74-7.73)	0.148	2.38 (0.67-8.50)	0.180
Before pregnancy	873	16.2	1.34 (0.92-1.97)	0.131	1.08 (0.60-1.94)	0.798

* Excluded from univariable and multivariable analyses.
N.B. ORs were adjusted for repeat pregnancies; AORs were adjusted for IDU-acquired infection, ethnic group, maternal age and clinical status.

Further analyses

Subgroup analyses

Information on some known risk factors for prematurity was not available in the NSHPC, including obstetric history (prior preterm delivery, history of miscarriage and stillbirth), socio-demographic factors and smoking in pregnancy (Slattery & Morrison, 2002). Demographic characteristics, including ethnic group and IDU, changed substantially over time (as shown in Chapter 3), and concurrent changes in the prevalence of other risk factors for prematurity are also likely to have occurred. Although it was not possible to control for these factors, the analyses were repeated for nulliparous and parous women, and for women who delivered in 1994-1999 and 2000-2005. The magnitude of the association was similar in nulliparous and parous women, and both were statistically significant (AOR=1.62, p=0.014, and AOR=1.61, p=0.026, respectively) (Table 5.8). The association between HAART and prematurity was also of similar magnitude in 1994-1999 (AOR=1.40, p=0.254) and in 2000-2005 (AOR=1.67, p=0.008), although due to the small sample size in the earlier period (n=489), the former was not statistically significant.

Sensitivity analyses

The effect of the inclusion criteria for this analysis on the findings were also explored by:

1. Excluding pregnancies in women on dual therapy (n=155)
2. Excluding stillbirths (n=49)

3. Excluding pregnancies in women who were on treatment at conception or in the first trimester of pregnancy (*n*=959), since early ART consisted mostly of HAART (94.4%, 914/968).

The association between HAART and prematurity was not substantially altered by excluding dual therapy (AOR=1.48, *p*=0.011), stillbirths (AOR=1.59, *p*=0.002) or pregnancies with early treatment (AOR=1.59, *p*=0.005) (Table 5.8).

Table 5.8 Subgroup and sensitivity analyses – adjusted odds ratios for the risk of premature delivery in women on HAART compared with mono/dual therapy

	n	**AOR**	**(95% CI)**	***p*-value**
Main adjusted model	**4407**	**1.63**	**(1.22-2.19)**	**0.001**
Pregnancies in nulliparous women	1391	1.61	(1.06-2.44)	0.026
Pregnancies in parous women	2614	1.62	(1.10-2.38)	0.014
Pregnancies in 1994-1999	489	1.40	(0.79-2.48)	0.254
Pregnancies in 2000-2005	3918	1.67	(1.14-2.44)	0.008
HAART and monotherapy only (excluding dual therapy)	4252	1.48	(1.09-2.01)	0.011
Live births only (excluding stillbirths)	4358	1.59	(1.18-2.14)	0.002
Treatment during pregnancy only (excluding early treatment)	3448	1.59	(1.15-2.19)	0.005

N.B. AORs are for HAART compared with mono/dual therapy (baseline omitted), and are adjusted for repeat pregnancies, IDU-acquired infection, ethnic group, maternal age and clinical status.

Birth weight

Mean birth weight was slightly but significantly lower for infants exposed to HAART *in utero* than for infants exposed to mono/dual therapy (2978 g versus 3096 g, respectively, $p<0.001$). To explore whether this difference was attributable to prematurity or whether infants were small for their gestational age, standard deviation scores (z-scores) for birth weight were derived. HAART-exposed infants were significantly lighter, after standardising for gestational age, than those exposed to mono/dual therapy (mean z-scores: HAART, -0.06; mono/dual therapy, 0.06, $p=0.002$). Results were similar for term (mean z-scores: HAART, -0.06; mono/dual therapy, 0.06, $p=0.003$, $n=3116$) and preterm infants (mean z-scores: HAART, -0.08; mono/dual therapy, 0.08, $p=0.329$, $n=469$), but not statistically significant for the premature group, probably due to sample size.

5.3 Comparative analysis of ART and prematurity in three studies

Despite growing evidence linking HAART with an increased risk of premature delivery over the last decade, several large-scale studies have failed to detect an association (Tuomala *et al.*, 2002; Tuomala *et al.*, 2005; Watts *et al.*, 2004a). There is ongoing debate about the reasons underlying these differences in findings, but no clear explanation has so far emerged (Thorne, Fiore, & Rudin, 2003; Tuomala & Yawetz, 2006). In response to this, a collaboration of three study groups (the PSD, ECS and NSHPC) was established, with the aim of exploring these differences. At the time this project was initiated, a recent ECS publication updating earlier findings from 2000 had indicated a two-fold increased risk of preterm delivery associated with HAART, compared with monotherapy or dual therapy (European Collaborative Study, 2004a). Preliminary analyses from the NSHPC suggested a similar risk for HIV-infected women in the UK and Ireland. Researchers from the PSD, a US monitoring study, were approached regarding a combined analysis. Preliminary findings from their study (published subsequently) suggested an increased risk of prematurity associated with PI-containing HAART, compared with dual therapy, the group with the lowest prematurity rate (Schulte *et al.*, 2007). These findings supported an association between treatment and prematurity, but with some differences. A comparative analysis was therefore carried out using data from the three studies.

Methodological differences

Study design

The three studies included in this project were chosen in part for their different methodologies, which were described briefly in Chapter 2. All three studies were observational, but varied in their approach. The ECS was the only study requiring enrolment and consent. A small survey carried out in 11 ECS centres in 2005 indicated that high enrolment rates were generally achieved: less than 5% (32/724) of eligible women in 2002-2004 were not enrolled, mostly because they moved away; none of the centres reported refusal as a reason for non-enrolment (Patel, 2007).

In both the PSD and NSHPC, births were included regardless of the timing of a woman's diagnosis or presentation for antenatal care. However, the PSD was restricted to US states with the highest prevalence of HIV. In some states the study only covered particular hospitals, and therefore did not necessarily include all births in a particular geographic area. For example, in Washington DC, Stanford (California) and North Carolina, the PSD covered only the large referral hospitals, where most women and children would have been seen. The other five sites – Puerto Rico, New York City, Massachusetts, Texas and California (Los Angeles County) – were more comprehensive, and included other hospitals and centres aside from the key referral centres; these sites were therefore considered 'population-based'. There were also changes in the sites over time; for instance, in Texas the PSD initially covered only a few cities, but was later extended to include others, although at no time were all cities included. The NSHPC, on the other hand, is a population-based surveillance study, which aims to include all HIV-infected pregnant women seeking

antenatal care in the UK and Ireland. Because the study relies on complementary paediatric and obstetric reporting systems, case ascertainment of infants born to HIV-infected women is high; over 90% of all HIV-infected women giving birth in England and Scotland are diagnosed by the time of delivery and reported to the NSHPC (Health Protection Agency, 2008).

In all three studies, women may have been excluded from the study hospitals due to issues around access to healthcare, either through lack of health insurance in the US, or due to language or social barriers experienced by recent immigrants in Europe. A recent report from France suggested that HIV-infected African women were more likely to present late for antenatal care, and be diagnosed late in pregnancy, than HIV-infected French women (Jasseron *et al.*, 2008), an issue that may also occur elsewhere in Europe.

None of the studies were set up specifically to investigate ART and premature delivery, but data on ART and gestational age were collected along with other maternal and pregnancy characteristics. Data in the PSD came mainly from paediatric medical records, with some input from maternal records where available, and was collected by trained CDC staff. In the NSHPC and ECS, forms were completed prospectively by clinicians and other health professionals, often those responsible for the women and children. Maternal and pregnancy data were therefore more complete in the ECS and NSHPC.

All three studies were observational, and decisions about type of treatment were based on a number of factors, including existing local or national guidelines, availability of antiretroviral drugs, and clinical indication. Different guidelines on the management of HIV infection in pregnancy are available in the US (Perinatal HIV Guidelines Working Group, 2008), Europe (Coll *et al.*, 2002), and the UK

(BHIVA/CHIVA, 2008), and guidelines were also updated periodically both in the US (Perinatal HIV Guidelines Working Group, 2005; Perinatal HIV Guidelines Working Group, 2008; Public Health Service Task Force, 1998; Public Health Service Task Force, 2002) and in the UK (BHIVA, 1999; BHIVA, 2001; BHIVA, 2005b; BHIVA/CHIVA, 2008). Differences in the way treatment was assigned are therefore likely, in terms of whether monotherapy, dual therapy or HAART was prescribed.

Variables

Similar information was collected in the three studies, but there were some differences in the range and definition of variables collected (Table 5.9). Variables that were consistent across the three studies included child's year of birth, mother's country of birth, gestational age and ART. ART was categorised as none, monotherapy, dual therapy, or HAART (three or more drugs), and HAART was classified as to whether PIs were included; combinations of three or more NRTIs were classified as non-PI HAART.

The prematurity variables used in the analyses (delivery at <37 weeks or <32 weeks gestation) were derived from actual gestational age (in completed weeks, as reported by clinicians) in all three studies. In the ECS, gestational age was based on an ultrasound scan if available (for the majority), and otherwise (rarely) on date of last menstrual period. In some ECS centres, especially in Germany (Grosch-Woerner *et al.*, 2008), planned caesarean sections are carried out at 36 weeks gestation; these cases were excluded from analyses where a 37 week cut-off was used, but included in the analyses involving a cut-off of 32 weeks gestation. In the PSD gestational age was as recorded in the paediatric notes, and in the NSHPC, as reported by

respondents. In the PSD, an additional binary (yes/no) variable for whether the child was preterm (defined as <37 weeks) was also available; in cases where gestational age was missing, this 'preterm' variable was used instead to classify infants with regard to prematurity. Where there were discrepancies between the two variables (n=177), actual gestational age was used; only nine cases were recorded as term but with a gestational age of <35 weeks.

Maternal region of birth was classified as within or outside the study region; for example, in the PSD, this referred to whether a woman was born in the US or not. Maternal ethnic origin was classified as white, black, Hispanic or other, with Hispanic only specified in the PSD. Information on IDU was collected in all three studies, but there were differences in the meaning of the variable between studies: in the PSD, history of IDU was recorded; in the ECS history or current use of IDU was based on self-report, evidence of drug withdrawal in the infants, and clinical observation; in the NSHPC, information on IDU related to whether it was the likely mode of acquisition of HIV. In addition, in the PSD and NSHPC, IDU was one of a number of risk factors for acquisition of HIV. If neither IDU, nor any other factors were given, the mother's risk factor was recorded as 'Other'; there are therefore no missing values. The ECS included a specific question on history of intravenous drug abuse (yes/no), and missing values were recorded as such. In the PSD, although information on maternal clinical status (HIV-related symptoms) at delivery was collected, no details of CD4 count or viral load were available. Because information on clinical status in the PSD related to the time of delivery, HIV-related symptoms or AIDS at delivery was used in the NSHPC.

Table 5.9 Summary of main differences between studies

	Pediatric Spectrum of HIV Disease project (PSD)	European Collaborative Study (ECS)	National Study of HIV in Pregnancy and Childhood (NSHPC)
Study Design	Review of paediatric medical records	Cohort study with enrolment	Confidential surveillance study
Coverage	Eight geographical sites; part population-based, part hospital-based	Over 25 centres in nine European countries	All maternity units in the UK and Ireland
Years included	1990-2004 (study concluded in 2004)	1990-2006	1990-2006
Maternal and pregnancy variables			
Ethnicity	Dataset included only white non-Hispanic, black non-Hispanic, Hispanic, and other (missing excluded)	White, black, other	White, black, other; child's ethnicity used if mother's not completed
Region of birth	Recorded as US, US Dependencies and Possessions, or other	Maternal country of birth	Maternal country of birth
Age at delivery (years)	Not available	Available	Available
Injecting drug use (IDU)	History of IDU, as reported in medical records	Self-reported history or current use of IDU	IDU as route of acquisition of HIV
Parity	Not available	Previous live births or stillbirths	Previous live births or stillbirths *
HIV symptoms	Available	Not routinely recorded (only for ~40% of mothers)	Available
Viral load and CD4 count	Not available	In pregnancy, nearest to delivery, up to one week after delivery	In pregnancy, nearest to delivery (viral load up to one week after delivery)
ART	Monotherapy, dual therapy, HAART with/without protease inhibitor	Monotherapy, dual therapy, HAART with/without protease inhibitor	Monotherapy, dual therapy, HAART with/without protease inhibitor
Mode of delivery	Vaginal or caesarean section	Vaginal, elective or emergency caesarean section	Vaginal, elective or emergency caesarean section

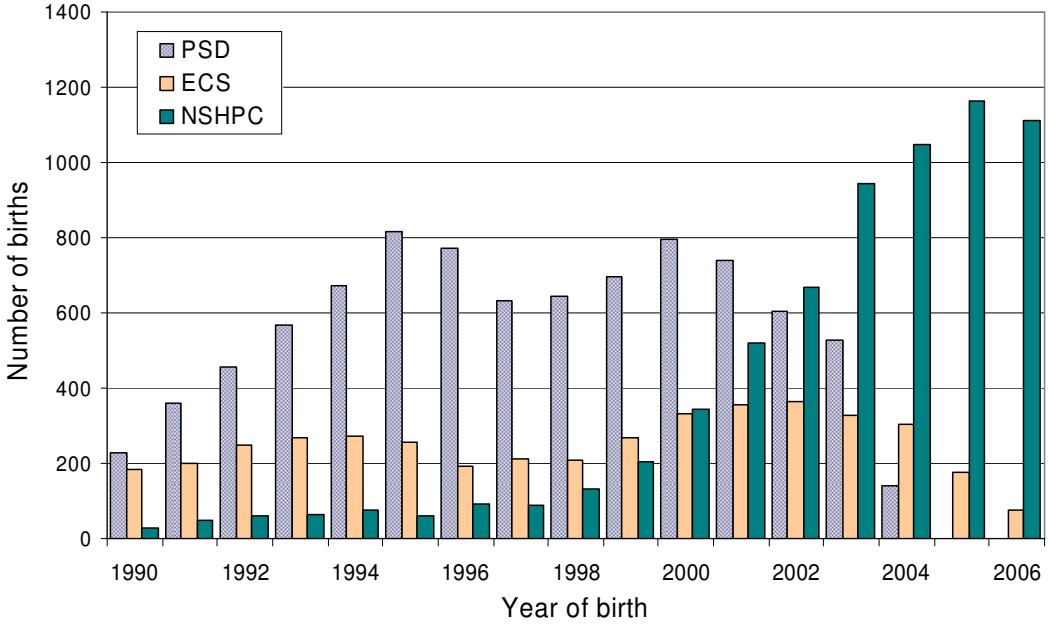
* For details, see page 58 (Chapter 2).

Population differences

Distribution of births over time

Figure 5.1 shows the distribution of births over time in the three studies. The skewed pattern seen in NSHPC births (described in Chapter 3) was driven both by an increase in HIV prevalence over time (particularly since 2000) and by an increase in the uptake of routine antenatal HIV screening, and reflects the actual number of diagnosed HIV-infected women giving birth in the UK and Ireland each year. The number of births in the PSD was influenced by the number of sites involved and their coverage; for instance, both North Carolina and Stanford ceased reporting after 1997 and 1998, respectively. Meanwhile, the number of cases from Texas increased from 34 in 1990 to 244 in 2002, as the PSD was expanded to include additional hospitals within the state. The number of cases from all sites declined after 2003, and the study concluded in 2004. In the ECS, the decline in number of cases in recent years reflects delayed reporting, as well as reduced enrolment from some centres. Enrolment from centres in the Ukraine increased in recent years, but these centres were not included in this analysis.

Figure 5.1 Distribution of births by year and study



Demographic characteristics

There was marked variation between studies in the baseline demographic characteristics of the mothers. The proportion of white mothers ranged from 9% in the PSD to 65% in the ECS, and the proportion of black mothers from 30% in the ECS to 81% in the NSHPC (Table 5.10). In the NSHPC, over 80% of mothers were born outside the study region, compared with about a third in the ECS and a fifth in the PSD (χ^2, df=2, p<0.001). There were also differences in the associations between characteristics; for example, black women in the PSD were predominantly US-born (83.3%, 3307/3971), whereas over 95% of those in the ECS (1174/1189) and NSHPC (5086/5242) were born abroad, mainly in sub-Saharan Africa.

Prevalence of maternal IDU was 13% in the PSD, 35% in the ECS, and 4% in the NSHPC (χ^2, df=2, p<0.001) (Table 5.10); IDU prevalence in the NSHPC may have been an underestimate compared with the other studies, since IDU referred to the route of HIV acquisition. In all three studies, IDU was more common in white women (Table 5.11); very low rates of IDU (<1%) were reported for black women in the ECS and NSHPC, with rates of around 9% for black women in the PSD.

In the PSD, maternal age was not available until after 2000 and was therefore not included in the analysis. However, age at delivery was available for the mothers of 1450 infants born since 2000; median maternal age was 28 years (IQR: 23-32 years). In the ECS, median maternal age was 27 years (IQR: 23-31 years) and in the NSHPC, 29 years (IQR: 26-33 years).

Table 5.10 Maternal demographic characteristics by study

Maternal characteristics		PSD *n*	PSD %	ECS *n*	ECS %	NSHPC *n*	NSHPC %
Region of birth	Within study region	5722	79.8	2613	61.4	987	14.8
	Outside study region	1445	20.2	1380	32.4	5473	82.1
	Total	**7167**		**3993**		**6460**	
	Missing	*1500*	*17.3*	*260*	*6.1*	*205*	*3.1*
Ethnic group	White	810	9.3	2673	65.4	1009	15.3
	Black	4849	55.9	1232	30.1	5350	81.1
	Hispanic	2743	31.6	0	0.0	0	0.0
	Other	265	3.1	183	4.5	237	3.6
	Total	**8667**		**4088**		**6596**	
	Missing	*0*	*0.0*	*165*	*3.9*	*69*	*1.0*
Injecting drug use	Non-IDU	7541	87.0	2650	64.6	6370	95.6
	IDU	1126	13.0	1453	35.4	295	4.4
	Total	**8667**		**4103**		**6665**	
	Missing	*0*	*0.0*	*150*	*3.5*	*0*	*0.0*
Age at delivery	14-19	0		113	2.9	230	3.5
(years)	20-24	0		681	17.2	1024	15.5
	25-34	0		2485	62.9	4221	64.1
	35-39	0		554	14.0	961	14.6
	≥40	0		120	3.0	154	2.3
	Total	**0**		**3953**		**6590**	
	Missing	*8667*	*100.0*	*300*	*7.1*	*75*	*1.1*
Parity	0	0		1931	48.2	1791	33.4
(live births	1	0		1228	30.6	1935	36.0
+ stillbirths)	2	0		538	13.4	974	18.1
	3 or more	0		313	7.8	670	12.5
	Total	**0**		**4010**		**5370**	
	Missing	*8667*	*100.0*	*243*	*5.7*	*1295*	*19.4*
Total*		**8667**		**4253**		**6665**	

* The overall total was used as the denominator for calculating the proportion of births with missing data on each of the variables; all other totals and proportions are based only on births with data available.

Table 5.11 Maternal injecting drug use by ethnic group and study

Maternal ethnic group	PSD *n*	PSD IDU *n* (%)	ECS *n*	ECS IDU *n* (%)	NSHPC *n*	NSHPC IDU *n* (%)
White	810	249 (30.7)	2612	1399 (53.6)	1009	270 (26.8)
Black	4849	419 (8.6)	1218	8 (0.7)	5350	15 (0.3)
Other	265	23 (8.7)	174	17 (9.8)	237	9 (3.8)
Hispanic	2743	435 (15.9)	0	-	0	-
χ^2 *p*-value	**(df=4)**	<0.001	**(df=2)**	<0.001	**(df=2)**	<0.001

df, degrees of freedom.

Treatment and pregnancy characteristics

Antiretroviral therapy

Overall differences between studies in the use of ART in pregnancy were apparent (Table 5.13, page 179); however, because of the differences over time in the distribution of births (Figure 5.1) and in the availability of ART, use of ART was explored in more detail over different time periods. General patterns of ART use over time were broadly similar across studies (Figures 5.2-5.4), although significant differences were also apparent. For example, uptake of zidovudine monotherapy was more rapid in the PSD than in the two European studies; in 1995, 83.8% (685/817) of mothers in the PSD were on monotherapy, compared with only 56.6% (145/256) in the ECS, and 58.0% (29/50) in the NSHPC (χ^2, df=2, p<0.001). Once dual therapy became available, it was also taken up faster in the PSD, with over a quarter of women (26.2%, 518/1975) on dual therapy between 1997 and 1999, compared with less than 20% in the ECS (18.0%, 124/688) and NSHPC (13.4%, 56/417; χ^2, df=2, p<0.001). Dual therapy remained more common in the PSD throughout the study period, and was used in around 15% of women between 2001 and 2004, compared with 10% in the ECS and 3% in the NSHPC (Table 5.12). Between 1998 and 2000, the proportion of women on HAART was similar in the three studies, increasing from around a third in 1998, to half in 1999, and 60% in 2000. Between 2001 and 2004, the proportion of mothers on HAART or monotherapy was higher in the NSHPC than in the ECS or PSD, and the proportion of women remaining untreated in pregnancy was lower (Table 5.12).

Table 5.12 Use of ART by study in 2001-2004

	PSD		ECS		NSHPC		χ^2 (df=2)
Type of ART	***n***	***%***	***n***	***%***	***n***	***%***	***p*-value***
Untreated	161	8.0	126	9.3	113	3.6	<0.001
Monotherapy	112	5.6	95	7.0	490	15.8	<0.001
Dual therapy	264	13.1	123	9.1	79	2.5	<0.001
HAART	1480	73.4	1009	74.6	2420	78.0	<0.001
Non-PI	*479*	*23.8*	*450*	*33.3*	*1505*	*48.5*	*<0.001*
PI	*1000*	*49.6*	*559*	*41.3*	*913*	*29.5*	*<0.001*
Total	2017	100.0	1353	100.0	3102	100.0	

* *p*-values are for each ART level compared with all others combined
N.B. Comparing PSD with ECS, differences in proportions of women who were untreated or on dual therapy were not statistically significant, nor was the difference in the overall proportion on HAART; other comparisons were statistically significant (p<0.001).

Of all pregnancies in women on monotherapy, 87.8% (2291/2608) occurred between 1990 and 1998 in the PSD, 72.4% (540/746) in the ECS, and 21.6% (209/969) in the NSHPC. Few pregnancies in women on HAART occurred before 1999: 11.3% (294/2605) in the PSD, 4.5% (73/1624) in the ECS, and 1.1% (53/4776) in the NSHPC. Comparisons between HAART and monotherapy in the PSD and ECS were therefore more historical than in the NSHPC, in which the majority of both HAART and monotherapy exposures occurred since 1999.

In all three studies, the majority of dual therapy regimens consisted of zidovudine and lamivudine: 81.1% (792/976) in the PSD, 74.7% (236/316) in the ECS, and 72.6% (130/179) in the NSHPC (χ^2=10.48, df=2, p=0.005). There were significant differences between studies in the use of HAART regimens, with PI-based regimens favoured in the PSD (67.6% of HAART regimens, 1000/1480) and ECS (55.4%, 559/1009), and non-PI regimens favoured in the NSHPC (62.2%, 1505/2418) (Table 5.13, page 179). It is also likely that the use of specific antiretroviral drugs differed between studies, partly due to differences in the distribution of cases over time; however, details of specific regimens were not available for comparison.

Figure 5.2 Use of ART over time in the PSD

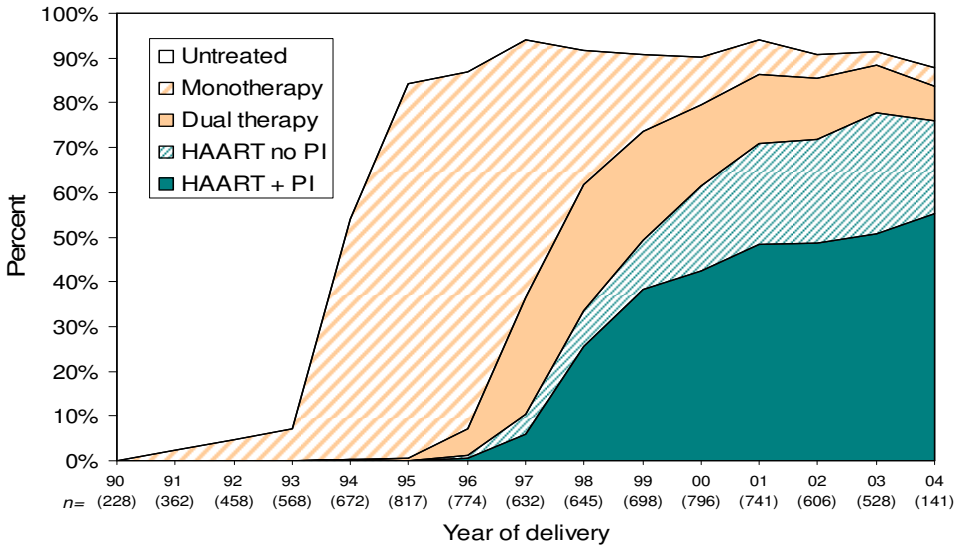


Figure 5.3 Use of ART over time in the ECS

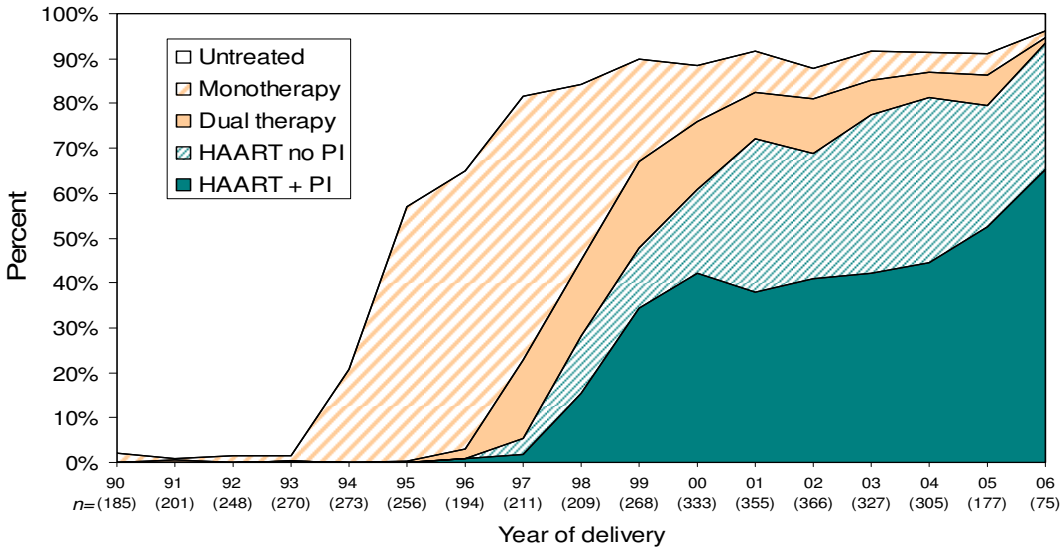


Figure 5.4 Use of ART over time in the NSHPC

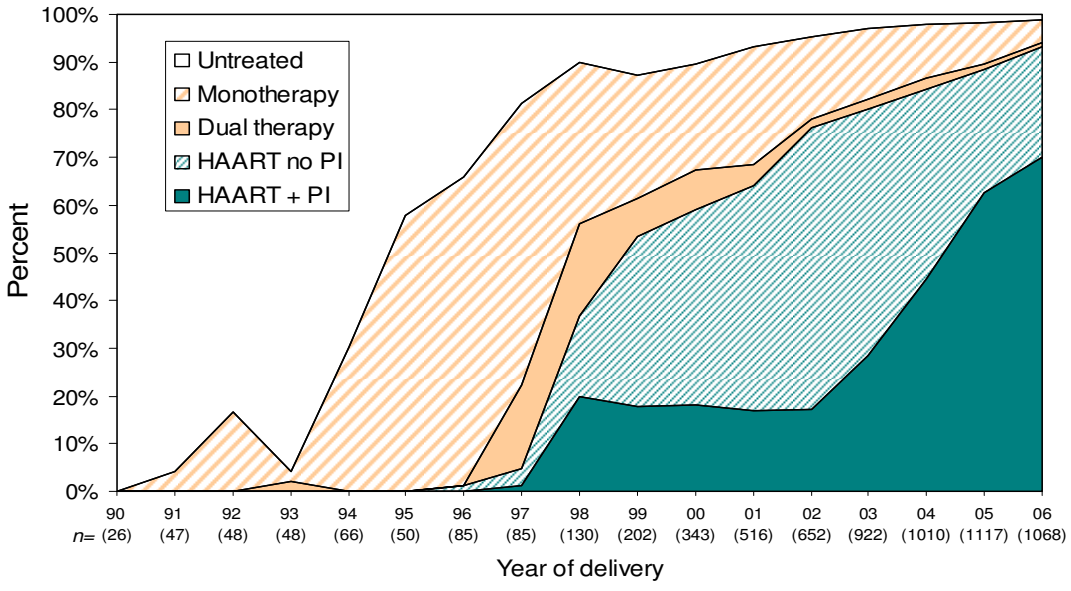


Table 5.13 Maternal pregnancy, clinical and treatment characteristics by study

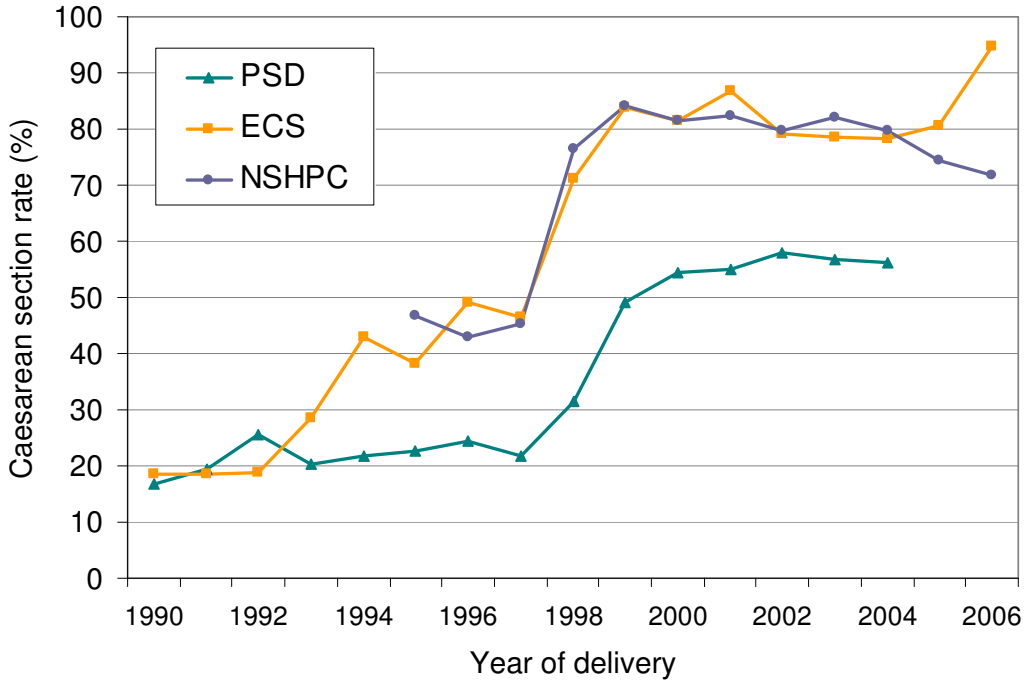
		PSD		ECS		NSHPC	
		n	*%*	*n*	*%*	*n*	*%*
ART	Untreated	2478	28.6	1567	36.8	492	7.7
	Monotherapy	2608	30.1	746	17.5	969	15.1
	Dual therapy	976	11.3	316	7.4	189	2.9
	HAART	2605	30.1	1624	38.2	4776	74.3
	Total	**8667**		**4253**		**6426**	
	Missing	*0*	*0.0*	*0*	*0.0*	*239*	*3.6*
Clinical status in pregnancy	No symptoms	4566	86.8	0		4942	92.0
	Symptoms	694	13.2	0		427	8.0
	Total	**5260**		**0**		**5369**	
	Missing	*3407*	*39.3*	*4253*	*100.0*	*1296*	*19.4*
CD4 cell count (cells/µl)	≥500	0		1190	39.7	1658	34.3
	350-499	0		762	25.4	1225	25.4
	200-349	0		683	22.8	1321	27.4
	<200	0		362	12.1	625	12.9
	Total	**0**		**2997**		**4829**	
	Missing	*8667*	*100.0*	*1256*	*29.5*	*1836*	*27.5*
Viral load (copies/ml)	<50	0		761	36.0	2660	55.2
	50-999 *	0		753	35.6	1166	24.2
	1000-9999	0		357	16.9	567	11.8
	≥10,000	0		243	11.5	430	8.9
	Total	**0**		**2114**		**4823**	
	Missing	*8667*	*100.0*	*2139*	*50.3*	*1842*	*27.6*
Mode of delivery	Caesarean section	3017	36.2	2486	59.8	4878	76.6
	Vaginal	5320	63.8	1673	40.2	1491	23.4
	Total	**8337**		**4159**		**6369**	
	Missing	*330*	*3.8*	*94*	*2.2*	*296*	*4.4*
Premature delivery (completed weeks)	≥37	7014	82.6	3385	85.1	5677	87.5
	<37	1482	17.4	592	14.9	808	12.5
	Total	**8496**		**3977**		**6485**	
	Missing	*171*	*2.0*	*276†*	*6.5*	*180*	*2.7*
Gestational age (completed weeks)	≥37	7014	83.2	3385	85.1	5677	87.5
	35-36	739	8.8	297	7.5	400	6.2
	32-34	434	5.1	192	4.8	238	3.7
	<32	247	2.9	103	2.6	170	2.6
	Total	**8434**		**3977**		**6485**	
	Missing	*233‡*	*2.7*	*276†*	*6.5*	*180*	*2.7*
	Total §	**8667**		**4253**		**6665**	

* Includes viral loads reported as '<200 copies/ml' or '<400 copies/ml.'
† Missing category (ECS) includes 175 elective caesarean section deliveries at 36 weeks gestation (see explanation on page 169).
‡ Missing category (PSD) includes 62 infants reported as 'preterm' but for whom actual gestational age was not provided; these 62 infants were included in the 'Premature delivery' variable (see explanation on page 182).
§ The overall total was used as the denominator for calculating the proportion of births with missing data on each of the variables; all other totals and proportions are based only on births with data available.

Mode of delivery

There were significant overall differences between studies in mode of delivery (Table 5.13, page 179). Overall caesarean section rates increased substantially between 1997 and 1999 in all three studies, but rates were lower throughout the study period in the PSD (Figure 5.5). In the ECS and NSHPC, rates increased from around 45% in 1995-1997 (ECS: 287/651; NSHPC: 97/217) to 81% from 1999 to 2004 (ECS: 1565/359; NSHPC: 3012/3719), while in the PSD, caesarean section rates were just over 20% (950/4283) up to 1997 and then rose to around 50% (333/679) in 1999, with a slight increase thereafter to about 58% (77/137) in 2004 (Figure 5.5).

Figure 5.5 Caesarean section rates over time by study



N.B Information on mode of delivery in the NSHPC was only available from 1995 onwards; the PSD concluded in 2004.

Maternal clinical and immunological characteristics

The proportion of women with HIV-related symptoms at delivery was higher in the PSD than in the NSHPC (13% versus 8%, $p<0.001$), but this was partly associated with the higher proportion of untreated women in the PSD; among women on HAART, the proportion of mothers with symptoms was similar: 7.7% (121/1564) in the PSD and 8.5% (333/3911) in the NSHPC ($p=0.346$). In the PSD, information on clinical status was only available for 40% of mothers, and there was wide variation between study sites in the proportion with missing information, from 10% (100/952) in Puerto Rico to 57% in New York (813/1419) and Texas (1347/2382).

Mothers in the ECS were less likely to have viral load <50 copies/ml than those in the NSHPC (Table 5.13), but this was mainly due to the higher proportion of recent births in the NSHPC, when uptake of treatment was high and the detection limit of most assays was <50 copies/ml. In 2005-2006, there was no significant difference between the two studies in the proportion of women with viral load <50 copies/ml: 70.6% (108/153) in the ECS, and 66.5% (1216/1828) in the NSHPC ($p=0.305$). Mothers in the ECS had higher CD4 cell counts (40% ≥500 cells/μl) than those in the NSHPC (34%, $p<0.001$).

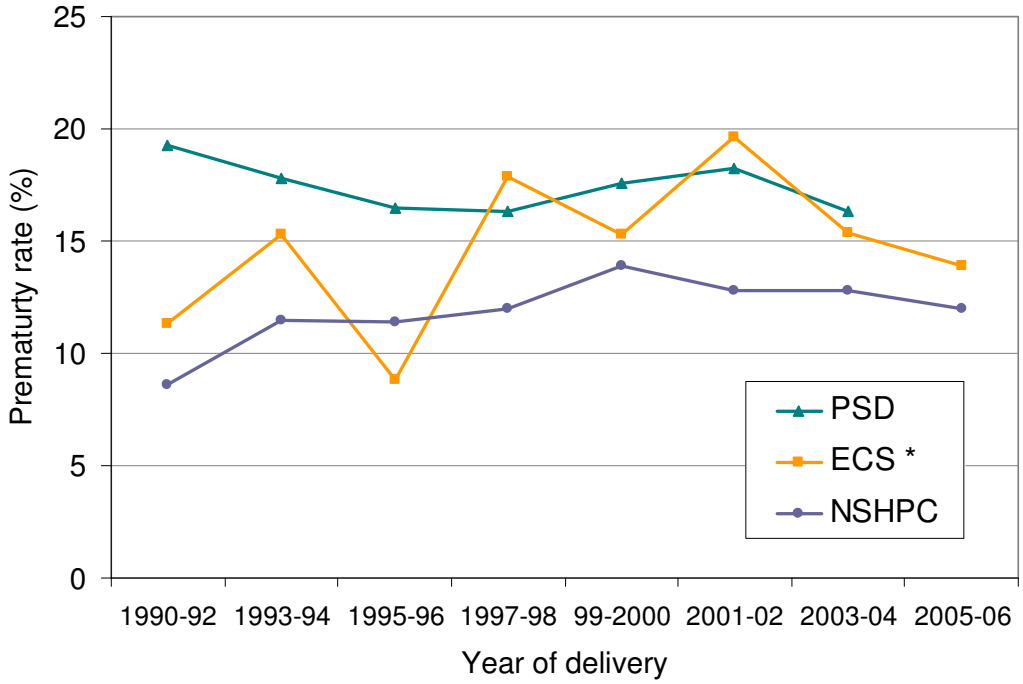
Prematurity rates and risk factors

Baseline prematurity rates and changes over time

Overall prematurity rates were 17.4% in the PSD, 14.9% in the ECS (after excluding 175 elective caesarean section deliveries at 36 weeks), and 12.5% in the NSHPC (Table 5.13, page 179) (p<0.001). There was no statistically significant change in prematurity rates over time in the PSD or NSHPC, but unadjusted rates in the ECS increased by an average of 3% per year (OR=1.03, 95% CI: 1.01-1.05, p=0.002) (Figure 5.6).

In the PSD, actual gestational age was missing for 20% of infants (1748/8667) but of these, 90% (1577/1748) had information on whether or not they were premature. Overall, term infants were less likely to have actual gestational age reported (78.4%, 5499/7014) than premature infants (95.8%, 1420/1482), so for the grouped gestational age variable (≥37, 35-36, 32-34, <32 weeks), the 1515 infants reported as 'term' were classified as ≥37 weeks. The 62 infants reported as 'preterm' were excluded from this variable: this led to a slight overestimate of the proportion of term infants (83.2%), compared with the prematurity variable (<37 weeks), in which they were included (82.6% were categorised as ≥37 weeks). The proportion of infants born at <32 weeks was 2.9% in the PSD, 2.5% in the ECS and 2.6% in the NSHPC (p=0.284).

Figure 5.6 Prematurity rates over time by study



* Excludes elective caesarean section deliveries carried out at 36 weeks (*n*=175).

Crude prematurity rates by ART

Prematurity rates by treatment in each of the three studies are shown in Table 5.14 and Figure 5.7. In unadjusted analyses, untreated women were 1.2, 1.3 and 1.5 times more likely to deliver prematurely in the PSD, ECS and NSHPC respectively, compared with those on monotherapy. Untreated women were not considered a suitable comparison group for two reasons:

1. As shown earlier (Chapter 5, page 148), premature delivery is likely to have prevented some women from initiating treatment, particularly in recent years, when uptake of ART was high; this is most likely to affect the NSHPC, in which over 85% of cases were reported since 2000.

2. Since a higher proportion of untreated women than treated women were reported in the pre-ART era, they were less likely to have information on CD4 count and symptoms reported. CD4 count was missing for 43.7% (684/1567) of untreated women, and 21.3% (572/2686) of treated women in the ECS ($p<0.001$), and for 59.3% (292/492) of untreated and 22.0% (1307/5934) of treated women in the NSHPC ($p<0.001$). Untreated women in the ECS were also more likely to have CD4 <200 cells/μl than treated women (14.8%, 131/883, versus 10.9%, 231/2114, $p=0.001$). In the PSD, untreated women were more likely to have missing information on symptoms (45.5%, 1127/2478, versus 36.8%, 2280/6189, $p<0.001$), and more likely to be symptomatic (21.5%, 290/1351, versus 10.3%, 404/3909, $p<0.001$) compared with treated women.

Compared with women on monotherapy, premature delivery was significantly less likely in women on dual therapy in the PSD (OR=0.79), and more likely in women

on HAART in the ECS (OR=1.60) and NSHPC (OR=1.28), but not in the PSD (OR=0.99) (Table 5.14).

Because of the significant differences in prematurity between the monotherapy and dual therapy groups in the PSD, these two groups were not combined in these analyses, although they were in the NSHPC analysis described in the previous section (5.2). Using dual therapy as a baseline, ORs for prematurity in women on HAART were 1.25 (95% CI: 1.01-1.54, p=0.039) in the PSD, 1.80 (95% CI: 1.21-2.67, p=0.004) in the ECS, and 1.51 (95% CI: 0.90-2.54, p=0.122) in the NSHPC. Although prematurity was lowest among women on dual therapy in all three studies, and the ORs were more homogeneous across studies than with monotherapy as the baseline, dual therapy was not selected as the reference group for the main analysis, because (1) only a small proportion of women were included in this group (particularly in the ECS and NSHPC); and (2) dual therapy is not a standard line of treatment and was mainly used during the transition from monotherapy to HAART in the mid- to late 1990s.

In the following analyses, monotherapy is used as the baseline and untreated women are excluded (n=2395 in the PSD, 1481 in the ECS and 482 in the NSHPC). A series of logistic regression models was developed; these models are summarised in Figure 5.8.

Table 5.14 Prematurity rates by ART

	ART	*n*	Prematurity rate	OR	(95% CI)	*p*-value
PSD	No ART	2395	20.2	1.24	(1.07-1.43)	0.003
(*n*=8496)	Monotherapy*	2552	16.9	1.00		
	Dual therapy	958	13.9	0.79	(0.64-0.98)	0.029
	HAART	2591	16.8	0.99	(0.85-1.14)	0.865
ECS	No ART	1481	14.7	1.30	(0.99-1.71)	0.058
(*n*=3977)	Monotherapy*	703	11.7	1.00		
	Dual therapy	294	10.5	0.89	(0.58-1.38)	0.611
	HAART	1499	17.5	1.60	(1.23-2.09)	0.001
NSHPC	No ART	482	14.3	1.46	(1.05-2.04)	0.023
(*n*=6291)	Monotherapy*	957	10.2	1.00		
	Dual therapy	181	8.8	0.85	(0.49-1.48)	0.565
	HAART	4671	12.8	1.28	(1.02-1.61)	0.031

* Baseline.

Figure 5.7 Prematurity rates by ART

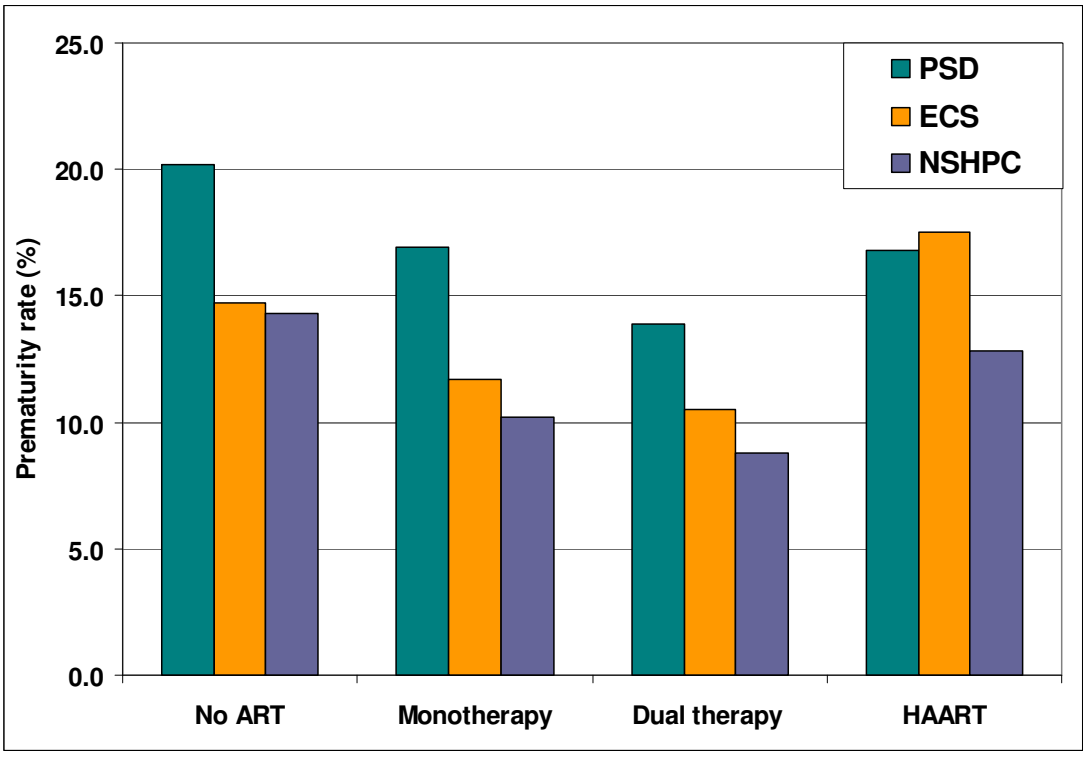
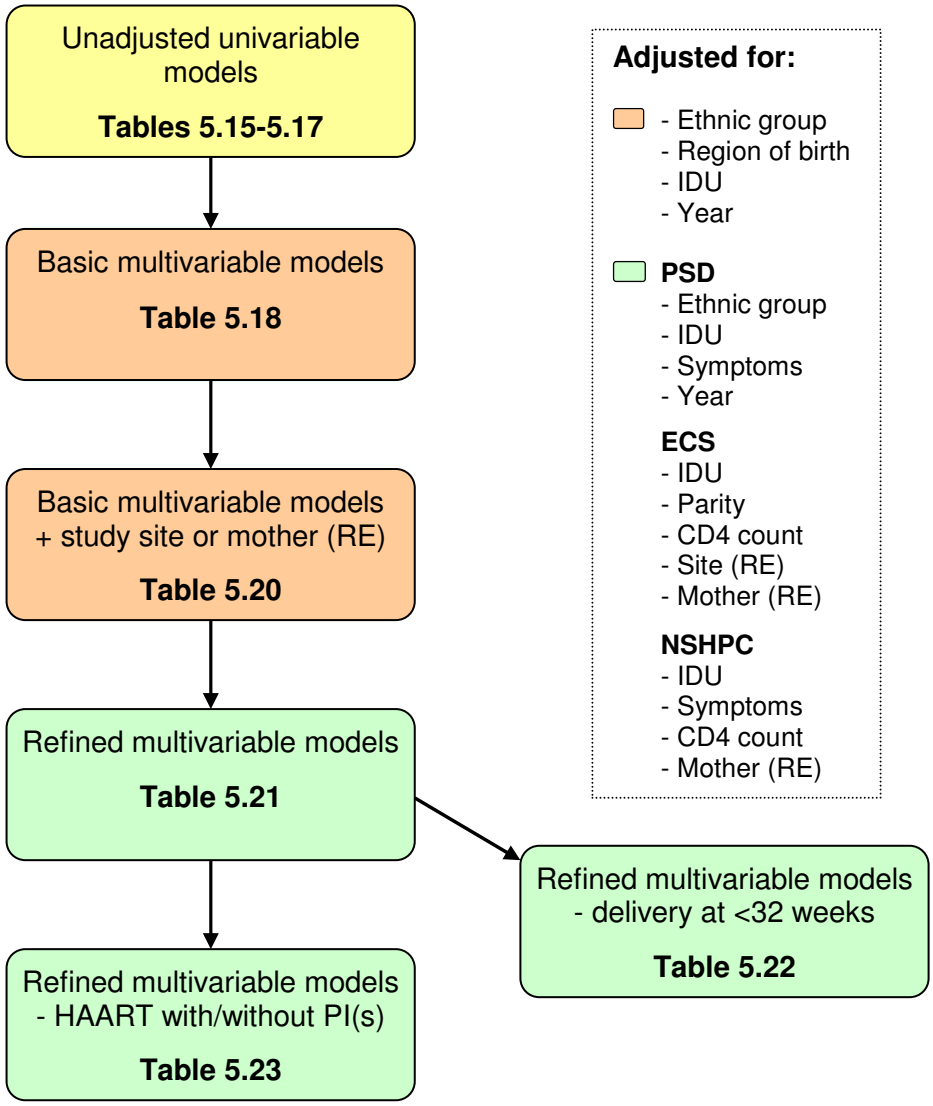


Figure 5.8 Flowchart showing logistic regression models for ART and prematurity in the PSD, ECS and NSHPC



Models	Model denominators (*n*) PSD	ECS	NSHPC
Unadjusted/univariable	6101	2496	5809
Basic multivariable	5056	2318	5722
Basic multivariable + study site	5056	2318	5722
Basic multivariable + mother	NA	2318	5424
Refined multivariable	3404	2367	4923
Refined multivariable <32 weeks	2783	2512	4785
Refined multivariable with/without PIs	3404	2367	4923

RE, random effect

Heterogeneity in the association between ART and prematurity

Heterogeneity between studies in the association between ART and prematurity was assessed using a weighted Mantel-Haenszel estimate for HAART compared with monotherapy, stratified by study. There was evidence of significant heterogeneity between studies (test of homogeneity of ORs: χ^2=11.63, df=2, p=0.009), suggesting that a summary estimate would not be appropriate. Separate logistic regression models were therefore developed for each individual study.

If, instead of monotherapy, dual therapy was used as a baseline, there was no significant heterogeneity between studies (test of homogeneity of ORs: χ^2=2.70, df=2, p=0.259), but if monotherapy and dual therapy were combined as a baseline, the association remained heterogeneous (test of homogeneity of ORs: χ^2=11.56, df=2, p=0.003).

Univariable risk factors for prematurity

Associations between prematurity and maternal characteristics are shown in Tables 5.15 (main variables) and 5.17 (variables only available in the ECS and NSHPC). In univariable analyses, ART was significantly associated with prematurity in all three studies (Table 5.15); however, in the PSD, the rate was lower in women on dual therapy than in those on monotherapy or HAART. In the ECS and NSHPC, rates were similar in women on monotherapy and dual therapy and higher in those on HAART (see also Figure 5.7, page 186). In the ECS and NSHPC, black women had lower rates of prematurity than white women (although the association was only borderline significant), and in the PSD there was no significant association with ethnic group.

Table 5.15 Rates and unadjusted odds ratios for prematurity in ART-treated women

			n	% pre-term	OR (95% CI)	*p*-value
PSD	***ART***	Monotherapy	2552	16.9	1.00	
		Dual therapy	958	13.9	0.79 (0.64-0.98)	0.029
		HAART	2591	16.8	0.99 (0.85-1.14)	0.865
	Ethnic origin	White	564	15.8	1.00	
		Black	3358	17.9	1.16 (0.91-1.48)	0.222
		Other	215	12.1	0.73 (0.46-1.17)	0.196
		Hispanic	1964	14.4	0.90 (0.69-1.16)	0.418
	Birth region	In study region	4063	17.0	1.00	
		Abroad	993	12.6	0.70 (0.57-0.86)	0.001
	IDU	Non-IDU	5520	15.5	1.00	
		IDU	581	24.3	1.74 (1.42-2.13)	<0.001
	Clinical status	No symptoms	3480	14.8	1.00	
		Symptoms	397	25.7	1.99 (1.56-2.53)	<0.001
	Year		6101		1.01 (0.99-1.03)	0.466
ECS	***ART***	Monotherapy	703	11.7	1.00	
		Dual therapy	294	10.5	0.89 (0.58-1.38)	0.611
		HAART	1499	17.5	1.60 (1.23-2.09)	0.001
	Ethnic origin	White	1354	16.2	1.00	
		Black	940	13.3	0.79 (0.63-1.01)	0.058
		Other	115	19.1	1.23 (0.75-1.99)	0.412
		Hispanic	0			
	Birth region	In study region	1310	16.5	1.00	
		Abroad	1047	13.8	0.81 (0.65-1.02)	0.077
	IDU	Non-IDU	1859	13.3	1.00	
		IDU	601	20.5	1.68 (1.32-2.13)	<0.001
	Clinical status	No symptoms	NA			
		Symptoms	NA			
	Year		2496		1.03 (1.00-1.07)	0.074
NSHPC	***ART***	Monotherapy	957	10.2	1.00	
		Dual therapy	181	8.8	0.85 (0.49-1.48)	0.565
		HAART	4671	12.8	1.28 (1.02-1.61)	0.031
	Ethnic origin	White	798	14.4	1.00	
		Black	4754	11.9	0.80 (0.64-0.99)	0.042
		Other	223	13.0	0.89 (0.57-1.37)	0.594
		Hispanic	0			
	Birth region	In study region	833	14.8	1.00	
		Abroad	4919	11.8	0.77 (0.62-0.95)	0.014
	IDU	Non-IDU	5620	11.9	1.00	
		IDU	189	22.2	2.12 (1.49-3.01)	<0.001
	Clinical status	No symptoms	4533	11.8	1.00	
		Symptoms	390	19.0	1.74 (1.33-2.28)	<0.001
	Year		5809		1.00 (0.96-1.03)	0.772

NA, not applicable.

IDU was strongly associated with prematurity in all three studies, with unadjusted ORs ranging from 1.7 to 2.1. Maternal age at delivery was available in the ECS and NSHPC; there was no evidence of a U-shaped association between maternal age and prematurity (Table 5.16), as reported for the general population (Slattery & Morrison, 2002), although this may have been due to small numbers. In the ECS, older mothers were marginally more likely to deliver prematurely than younger mothers (Table 5.17). Parity was not associated with prematurity in the NSHPC, but in the ECS, prematurity rates were higher among parous than nulliparous women (Table 5.17).

Table 5.16 Maternal age and prematurity in ART-treated women

Maternal age (years)	*n*	Prematurity rate	OR	(95% CI)	*p*-value
ECS					
14-19	56	10.7	0.73	(0.30-1.74)	0.473
20-24	321	13.4	0.94	(0.64-1.38)	0.737
25-29*	684	14.2	1.00		
30-34	765	15.7	1.13	(0.84-1.50)	0.423
35-39	424	18.4	1.36	(0.98-1.89)	0.062
≥40	101	13.9	0.97	(0.53-1.78)	0.931
NSHPC					
14-19	200	11.5	1.03	(0.65-1.62)	0.904
20-24	859	11.6	1.04	(0.81-1.34)	0.744
25-29*	1908	11.2	1.00		
30-34	1776	12.8	1.17	(0.96-1.42)	0.130
35-39	896	13.8	1.27	(1.00-1.61)	0.047
≥40	141	11.4	1.01	(0.59-1.74)	0.962

* Baseline.

Table 5.17 Rates and unadjusted odds ratios for prematurity in ART-treated women in the ECS and NSHPC

	ECS				NSHPC			
	n	% pre-term	OR (95% CI)	*p* - value	*n*	% pre-term	OR (95% CI)	*p* - value
Maternal age (years)								
<25	377	13.0	1.00		1059	11.6	1.00	
25-34	1449	15.0	1.18 (0.85-1.65)	0.332	3684	12.0	1.04 (0.84-1.28)	0.734
≥35	525	17.5	1.42 (0.98-2.07)	0.066	1037	13.5	1.19 (0.92-1.54)	0.193
Parity (live births + stillbirths)								
0	1106	12.7	1.00		1705	12.8	1.00	
1	748	15.9	1.31 (1.00-1.70)	0.048	1772	11.7	0.90 (0.74-1.11)	0.321
2	343	19.0	1.61 (1.17-2.23)	0.004	895	12.3	0.95 (0.74-1.21)	0.686
3 or more	198	17.7	1.48 (0.99-2.22)	0.058	584	13.0	1.02 (0.77-1.34)	0.916
CD4 count (cells/µl)								
≥500	762	11.0	1.00		1593	10.5	1.00	
350-499	527	13.5	1.26 (0.90-1.76)	0.185	1163	11.4	1.10 (0.87-1.40)	0.428
200-349	464	18.5	1.84 (1.33-2.54)	<0.001	1275	12.5	1.23 (0.97-1.54)	0.084
<200	207	21.3	2.18 (1.46-3.26)	<0.001	596	14.8	1.48 (1.12-1.95)	0.006
Missing	536	16.8	1.63 (1.18-2.24)	0.003	1182	13.7	1.36 (1.08-1.71)	0.010
Viral load (copies/ml)								
<50	692	13.2	1.00		2646	10.1	1.00	
50-999	524	16.8	1.33 (0.97-1.83)	0.076	1139	12.6	1.28 (1.03-1.59)	0.023
1000-9999	252	17.5	1.40 (0.94-2.07)	0.095	537	16.4	1.75 (1.35-2.28)	<0.001
≥10,000	153	20.3	1.68 (1.07-2.64)	0.025	384	16.1	1.72 (1.28-2.33)	<0.001
Missing	875	13.8	1.06 (0.79-1.42)	0.697	1103	13.7	1.42 (1.15-1.76)	0.001

* Includes viral loads reported as '<200 copies/ml' or '<400 copies/ml' (*n*=336 in the ECS; *n*=162 in the NSHPC)

Maternal clinical status at delivery was strongly associated with prematurity in both the PSD and NSHPC with ORs of 2.0 and 1.7 respectively, for symptomatic compared with asymptomatic women (Table 5.15, page 189). A comparable variable was only available for about 40% of ECS mothers, but CD4 cell count, a related variable, was available for about 78% of mothers in both the ECS (2114/2686) and NSHPC (4627/5934). In the NSHPC, although mothers with low CD4 count (<200 cells/µl) were over 3.5 times more likely to have HIV-related symptoms reported than those with high CD4 count (≥500 cells/µl) (16.8%, 93/555, versus 5.1%, 76/1490), over 80% of all those with low CD4 count were asymptomatic. Compared with a CD4 count of ≥500 cells/µl, CD4 <200 cells/µl was associated with a two-fold increased risk of prematurity in the ECS, and a 1.5-fold increased risk in the NSHPC (Table 5.17). Prematurity rates among those with missing CD4 count were not significantly different from those with CD4 reported: 16.8% (90/536) versus 14.5% (285/1960) in the ECS (p=0.196), and 13.7% (162/1182) versus 11.8% (548/4627) in the NSHPC (p=0.081). High viral load was also associated with a significantly increased risk of prematurity (Table 5.17).

Multivariable risk factors for prematurity

Basic multivariable logistic regression models were developed (Figure 5.8, page 187), initially including only covariates common to all three studies (ART, ethnic group, region of birth, IDU and year) (Table 5.18). Year of delivery was considered a possible confounder because underlying trends in the baseline prematurity rate could result from changes over time in unmeasured risk factors for prematurity, such as the prevalence of other sexually transmitted infections.

ART was independently associated with prematurity in all three studies after adjusting for ethnicity, region of birth, IDU and year of delivery; however, in the PSD dual therapy was associated with a significantly reduced risk of prematurity compared with monotherapy (AOR=0.76), while in the ECS and NSHPC, HAART was associated with a significantly increased risk of prematurity (AOR=1.79 and 1.38, respectively) (Table 5.18). The increased risk of prematurity (AOR=1.35) among black women in the PSD became significant only after adjusting for other risk factors, whereas in the ECS and NSHPC, the borderline association with ethnicity disappeared in the adjusted models, probably because it was driven by high rates of IDU in white women (shown in Table 5.11, page 175). Being born outside the study region was associated with a reduced risk of prematurity in all three studies; however, because of the substantial overlap between maternal ethnic origin and region of birth in the ECS and NSHPC (as described earlier, page 174), this association lost significance in the adjusted models. In all three studies, IDU was strongly associated with prematurity, with AORs ranging from 1.8-2.2; adjusting for ART, ethnicity, region of birth and year led to an increase in the ORs for IDU (Table 5.18), due to the association between IDU and ethnic group in the PSD (Table 5.11, page 175), and IDU and ART in the NSHPC (Table 5.1, page 149) and ECS. In the PSD, year of delivery was not associated with prematurity in univariable analysis, but in the adjusted model was associated with a borderline significant 4% increase in prematurity per year (p=0.055). In the ECS, the borderline association between year of delivery and prematurity in univariable analysis was removed by adjusting for other risk factors.

Table 5.18 Unadjusted and adjusted odds ratios for prematurity in ART-treated women (basic models)

		Univariable		Multivariable	
		OR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
PSD	***ART***	**(*n*=6101)**		**(*n*=5056)**	
	Monotherapy	1.00		1.00	
	Dual therapy	0.79 (0.64-0.98)	0.029	0.76 (0.59-0.98)	0.037
	HAART	0.99 (0.85-1.14)	0.865	0.88 (0.69-1.13)	0.326
	Ethnic origin				
	White	1.00		1.00	
	Black	1.16 (0.91-1.48)	0.222	1.35 (1.03-1.77)	0.027
	Other	0.73 (0.46-1.17)	0.196	1.00 (0.59-1.70)	0.993
	Hispanic	0.90 (0.69-1.16)	0.418	1.02 (0.76-1.35)	0.918
	Region of birth				
	In study region	1.00		1.00	
	Abroad	0.70 (0.57-0.86)	0.001	0.77 (0.62-0.96)	0.018
	IDU				
	Non-IDU	1.00		1.00	
	IDU	1.74 (1.42-2.13)	<0.001	1.88 (1.49-2.37)	<0.001
	Year	1.01 (0.99-1.03)	0.466	1.04 (1.00-1.08)	0.055
ECS	***ART***	**(*n*=2496)**		**(*n*=2318)**	
	Monotherapy	1.00		1.00	
	Dual therapy	0.89 (0.58-1.38)	0.611	0.93 (0.57-1.50)	0.754
	HAART	1.60 (1.23-2.09)	0.001	1.79 (1.24-2.60)	0.002
	Ethnic origin				
	White	1.00		1.00	
	Black	0.79 (0.63-1.01)	0.058	1.27 (0.61-2.65)	0.516
	Other	1.23 (0.75-1.99)	0.412	1.91 (0.87-4.20)	0.107
	Hispanic	NA		NA	
	Region of birth				
	In study region	1.00		1.00	
	Abroad	0.81 (0.65-1.02)	0.077	0.74 (0.36-1.52)	0.411
	IDU				
	Non-IDU	1.00		1.00	
	IDU	1.68 (1.32-2.13)	<0.001	1.83 (1.36-2.46)	<0.001
	Year	1.03 (1.00-1.07)	0.074	1.00 (0.95-1.05)	0.958
NSHPC	***ART***	**(*n*=5808)**		**(*n*=5722)**	
	Monotherapy	1.00		1.00	
	Dual therapy	0.85 (0.49-1.48)	0.565	0.78 (0.45-1.37)	0.386
	HAART	1.28 (1.02-1.61)	0.031	1.38 (1.08-1.77)	0.011
	Ethnic origin				
	White	1.00		1.00	
	Black	0.80 (0.64-0.99)	0.042	1.19 (0.82-1.73)	0.355
	Other	0.89 (0.57-1.37)	0.594	1.27 (0.76-2.11)	0.360
	Hispanic	NA		NA	
	Region of birth				
	In study region	1.00		1.00	
	Abroad	0.77 (0.62-0.95)	0.014	0.76 (0.54-1.07)	0.111
	IDU				
	Non-IDU	1.00		1.00	
	IDU	2.12 (1.49-3.01)	<0.001	2.16 (1.43-3.26)	<0.001
	Year	1.00 (0.96-1.03)	0.772	0.98 (0.95-1.02)	0.314

Multivariable AORs adjusted for ART, maternal ethnic origin, region of birth, IDU and year.

Interactions between ART and other risk factors

Interactions between ART and other variables were assessed first using stratified Mantel-Haenszel ORs, and then through the addition of interaction terms to the multivariable logistic regression models presented in Table 5.18. There was no evidence of any significant interactions in the ECS or NSHPC. In the PSD, there was some evidence of an interaction between ART and maternal ethnicity (test of homogeneity of ORs: p=0.0217): in univariable analysis, white and Hispanic women tended to be more likely to deliver prematurely if they were on HAART than if they were on monotherapy, while black women and those of other ethnic groups tended to be less likely to deliver prematurely (Table 5.19). Stratified odds ratios were calculated for each ethnic group separately. After adjusting for IDU and year, the differences in the association between ART and prematurity across ethnic groups were less clear (Table 5.19). The increased unadjusted OR for the association between ART and prematurity among white women in the PSD was explained by differences in prematurity rates over time in this group, possibly relating to changes in the risk profile of these women. Rates were 13.0% (78/601) before 2000, when monotherapy was more common, and 23.6% (46/195) in 2000-2004 (p<0.001), when HAART was more common; however, within each time period there was no association between HAART and prematurity.

Table 5.19 ART and prematurity stratified by ethnic group in the PSD

		HAART versus monotherapy			
	n	**OR (95% CI)**	***p*-value**	**AOR (95% CI)**	***p*-value**
Ethnic group					
White	470	1.55 (0.94-2.57)	0.087	0.74 (0.35-1.56)	0.427
Black	2829	0.86 (0.71-1.04)	0.122	0.81 (0.61-1.08)	0.148
Hispanic	1668	0.46 (0.18-1.20)	0.111	0.44 (0.13-1.45)	0.177
Other	176	1.20 (0.92-1.56)	0.186	1.17 (0.77-1.77)	0.460

* Adjusted for injecting drug use and year

Effect of study site and repeat pregnancies

All three studies were set across wide geographical areas, covering different countries, states and regions, and data were collected from different sites. The PSD included eight sites, distributed across seven US states, the ECS included 30 centres distributed across nine countries, and NSHPC data came from 205 hospitals distributed across 14 countries or regions (Ireland, Northern Ireland, Scotland, Wales, and 10 English regions). Differences in the HIV epidemiology, baseline population characteristics and clinical practice between areas included within a study may also be associated with variation in unmeasured baseline risk factors for prematurity. For example, in the PSD there were substantial differences in maternal ethnicity between the eight study sites: almost all mothers in Puerto Rico (99.8%) were Hispanic, as were half of mothers in California, whereas in New York and North Carolina, 80-85% of women were black. Although it was possible to control for ethnicity in the analysis, these disparities suggest that there may be differences in other, unmeasured risk factors for prematurity between sites (e.g. socio-demographic factors, smoking, parity, etc). In order to address this potential variation, models were fitted including a random effect term for study site, which adjusts for differences between sites attributable to unobserved variables (Rabe-Hesketh, Skrondal, & Pickles, 2002). Study site referred to PSD site, ECS study centre and NSHPC hospital. In addition, NSHPC and ECS models were adjusted for repeat pregnancies, using a random effect term for maternal identity.

In the PSD, the random effect term for study site was significant only in the unadjusted model, suggesting that although there were baseline differences in prematurity between sites, they were explained by the variables included in the

multivariable model (Table 5.20); ORs for the association between ART and prematurity were not altered by the inclusion of random effect terms in either the univariable or the multivariable model. In the ECS, including a term for study centre significantly improved both the univariable and multivariable models (Table 5.20), as assessed by LRTs, and caused the OR and AOR for the association between ART and prematurity to increase by 10-15%. Including a random effect term on NSHPC hospital had very little effect on the overall estimates and did not improve the models (Table 5.20), nor did fitting a term on UK region/country (n=14; LRT, p=1.000).

In the ECS and NSHPC, it was also possible to adjust for effects associated with repeat pregnancies, using a random effect term on maternal identity. This significantly improved the models in both the ECS and NSHPC (Table 5.20). In the ECS, adjusting for unmeasured effects attributable to the mother led to over a 30% increase in the ORs (OR: 1.60 to 2.13; AOR: 1.79 to 2.36) for the association between ART and prematurity, whereas in the NSHPC, there was only a moderate (<10%) increase in the ORs.

Table 5.20 Logistic regression models for ART and prematurity including random effects on study site and mother

HAART vs. monotherapy	Univariable OR (95% CI)	*p* -value	*p* -value (LRT)**	Multivariable* AOR (95% CI)	*p* -value	*p* -value (LRT)**
PSD						
Basic model	0.99 (0.85-1.14)	0.865		0.88 (0.69-1.13)	0.326	
+ site (RE)	0.99 (0.85-1.15)	0.895	0.008	0.89 (0.69-1.13)	0.335	0.372
ECS						
Basic model	1.60 (1.23-2.09)	0.001		1.79 (1.24-2.60)	0.002	
+ site (RE)	1.78 (1.33-2.37)	<0.001	<0.001	2.17 (1.46-3.22)	<0.001	<0.001
+ mother (RE)	2.13 (1.35-3.36)	0.001	<0.001	2.36 (1.30-4.29)	0.005	<0.001
NSHPC						
Basic model	1.28 (1.02-1.61)	0.031		1.38 (1.08-1.77)	0.011	
+ site (RE)	1.28 (1.02-1.61)	0.031	0.490	1.38 (1.08-1.77)	0.011	0.491
+ mother (RE)	1.34 (1.00-1.78)	0.048	<0.001	1.48 (1.08-2.02)	0.015	<0.001

LRT, likelihood ratio test; RE, random effects.
All models included three levels of ART (monotherapy, dual therapy and HAART), but only odds ratios for HAART compared with monotherapy are shown.
* Adjusting for maternal ethnic origin, region of birth, IDU, and year of delivery.
** *p*-value relates to LRT for inclusion of random effect term.

Risk factors for prematurity adjusting for clinical and immunological factors

Logistic regression models were then expanded to include the additional covariates that were not available for all of the studies – maternal age, parity, clinical status and CD4 count – as well as the random effect terms, where appropriate. The optimal model was then selected for each study, based on inclusion of each covariate and assessment with LRTs (Table 5.21).

Factors significantly and consistently associated with prematurity in all the models (where available) included ART, IDU, clinical status and CD4 count. Compared with monotherapy, HAART was associated with a two-fold and 1.5-fold increased risk of prematurity in the ECS and NSHPC respectively, and dual therapy with 25% reduction in risk in the PSD; HAART was not associated with prematurity in the PSD when monotherapy was used as the baseline group. Despite differences between studies in the way IDU was measured and in the proportion of women with IDU reported, there was a consistent two-fold increased risk of prematurity associated with this group in all three studies. Maternal HIV symptoms were associated with a 1.9-fold increased risk of prematurity in both the PSD and NSHPC. Because the inclusion of symptoms in the PSD model reduced the sample by about a third (from 6101 to 3877), an alternative model was fitted with three levels for clinical status: asymptomatic, symptomatic and missing. Results were very similar (AOR for HAART versus monotherapy = 0.88, 95% CI: 0.70-1.09, p=0.243), and having missing information on symptoms was not associated with an increased risk of prematurity (AOR=1.12, 95% CI: 0.96-1.31, p=0.141). Low CD4 cell count was also consistently associated with prematurity, but the AOR was greater and more highly

significant in the ECS (AOR=2.47 for CD4 <200 cells/μl compared with ≥500 cells/μl, $p<0.001$) than in the NSHPC (AOR=1.54, $p=0.028$).

Maternal age was not significantly associated with prematurity in either the ECS or the NSHPC and was therefore excluded from the models. Maternal ethnic group, region of birth and year of delivery were not significant risk factors in the ECS or NSHPC, after adjusting for other factors, but black ethnicity remained significantly associated with prematurity in the PSD model (AOR=1.55, compared with white ethnicity), and baseline prematurity rates increased by an average of 5% per year (AOR=1.05), irrespective of other measured risk factors (Table 5.21). Parity was significantly associated with prematurity in the ECS but not the NSHPC; because prematurity rates were similar in women with one, two, or at least three previous live births or stillbirths, parity was recoded as a binary variable. The ECS model was adjusted for random effects attributable to the study site and to the mother, and the NSHPC model for random effects attributable to the mother.

Although in the ECS and NSHPC viral load was also significantly associated with prematurity in univariable analyses, models were not adjusted for both viral load and CD4 count, due to collinearity. However, adjusting for viral load instead of CD4 count (in addition to the covariates shown in Table 5.21) yielded similar results in the ECS, with an AOR of 2.90 (95% CI: 1.68-4.99, $p<0.001$, $n=2460$) for the association between HAART and prematurity, compared with monotherapy; in the NSHPC, the AOR increased from 1.47 in the model with CD4 count (Table 5.21) to 2.14 (95% CI: 1.51-3.03, $p<0.001$, $n=4923$) in the model with viral load.

Table 5.21 Significant risk factors for prematurity; results of logistic regression models developed separately for each study

		n	AOR	95% CI	*p* -value
PSD (*n* =3404)					
ART	Monotherapy	1659	1.00		
	Dual therapy	661	0.74	(0.54-1.02)	0.067
	HAART	1557	0.92	(0.67-1.26)	0.598
Ethnic origin	White	439	1.00		
	Black	1758	1.55	(1.13-2.12)	0.006
	Other	103	1.19	(0.59-2.36)	0.629
	Hispanic	1577	1.08	(0.78-1.49)	0.655
Region of birth	United States	3418	1.00		
	Elsewhere	459	0.77	(0.59-1.00)	0.053
IDU	Non-IDU	3418	1.00		
	IDU	459	1.97	(1.51-2.57)	<0.001
Maternal symptoms	Asymptomatic	3480	1.00		
	Symptomatic/AIDS	397	1.99	(1.53-2.59)	<0.001
Year of delivery	Per year	3877	1.05	(1.00-1.11)	0.053
ECS (*n* =2367)					
ART	Monotherapy	662	1.00		
	Dual therapy	277	0.80	(0.36-1.75)	0.571
	HAART	1428	2.92	(1.53-5.56)	0.001
IDU	Non-IDU	1795	1.00		
	IDU	572	3.78	(1.84-7.78)	<0.001
Parity	Nulliparous	1832	1.00		
	Parous	535	2.27	(1.27-4.02)	0.005
CD4 count (cells/µl)	≥500	723	1.00		
	350-499	497	1.45	(0.79-2.64)	0.232
	200-349	438	2.53	(1.23-5.19)	0.012
	<200	200	4.46	(1.69-11.72)	0.002
	missing	509	2.34	(1.13-4.88)	0.023
Centre (random effect)	constant	31 groups	1.00	(0.59-1.73)	<0.001*
Mother (random effect)	constant	2180 groups	4.46	(1.25-4.65)	<0.001*
NSHPC (*n* =4923)					
ART	Monotherapy	874	1.00		
	Dual therapy	138	0.55	(0.24-1.29)	0.169
	HAART	3911	1.47	(1.07-2.02)	0.017
IDU	Non-IDU	4794			
	IDU	129	2.13	(1.13-3.99)	0.019
Maternal symptoms	Asymptomatic	4533			
	Symptomatic/AIDS	390	1.87	(1.28-2.73)	0.001
CD4 count (cells/µl)	≥500	1490			
	350-499	1108	1.09	(0.79-1.49)	0.604
	200-349	1184	1.24	(0.91-1.70)	0.168
	<200	555	1.54	(1.05-2.26)	0.028
	missing	586	1.84	(1.26-2.70)	0.002
Mother (random effect)	constant	4333 groups	0.44	(0.27-0.61)	<0.001*

* *p*-value for likelihood ratio test for inclusion of random effect terms.

ART and severe prematurity (<32 weeks)

The association between ART and severe prematurity (<32 weeks) was also investigated. Similar models to those in Table 5.21 were fitted, but due to the fact that very few women had more than one delivery at <32 weeks (three in the ECS, four in the NSHPC), the ECS and NSHPC models were not adjusted for repeat pregnancies. As shown previously in the NSHPC (page 160), the association between HAART and prematurity was stronger when 32 weeks was used as a cut-off, with about a two-fold increase in severe prematurity both in univariable and multivariable analysis, adjusting for IDU, clinical status and CD4 count (Table 5.22). Due to small numbers, the dual therapy group in the NSHPC was omitted from the model. In the ECS, HAART was associated with over a 3.5-fold increase in severe prematurity, after adjusting for IDU, parity, CD4 count and centre. In the PSD, however, severe premature delivery was reduced in women on dual therapy or HAART compared with monotherapy, although this was only of borderline significance (Table 5.22).

Table 5.22 ART and severe prematurity (<32 weeks gestation)

		Univariable			Multivariable*		
	% <32 weeks	*n* (OR)	OR (95% CI)	*p* -value	*n* (AOR)	AOR (95% CI)	*p* -value
PSD							
Monotherapy	2.8	2537	1.00		1427	1.00	
Dual therapy	2.3	957	0.82 (0.50-1.33)	0.414	605	0.50 (0.24-1.05)	0.065
HAART	2.5	2570	0.89 (0.63-1.25)	0.493	1356	0.51 (0.25-1.04)	0.065
ECS							
Monotherapy	1.0	733	1.00		690	1.00	
Dual therapy	1.6	308	1.71 (0.54-5.43)	0.362	291	1.00 (0.26-3.92)	0.996
HAART	3.5	1604	3.75 (1.70-8.27)	0.001	1531	3.73 (1.67-8.32)	0.001
NSHPC							
Monotherapy	1.4	957	1.00		874	1.00	
Dual therapy	1.1	181	0.81 (0.18-3.63)	0.784	-	-	
HAART	2.6	4671	1.93 (1.09-3.44)	0.025	3911	2.06 (1.09-3.88)	0.026

* AORs in the PSD adjusted for maternal ethnicity, region of birth, IDU, symptoms and year of delivery; in the ECS for IDU, CD4 count, and site; and in the NSHPC for IDU, symptoms and CD4 count.
N.B. Dual therapy was dropped from the NSHPC multivariable model due to small numbers.

Protease inhibitors

Both PI- and non-PI-based HAART were associated with an increased risk of prematurity in the ECS and NSHPC, compared with monotherapy (Table 5.23). Prematurity rates in the PSD were slightly higher with PI-based HAART (17.3%) than with non-PI-based HAART (15.5%), but the difference was not statistically significant (p=0.251).

Table 5.23 ART and prematurity: HAART with and without protease inhibitors

			Univariable		Multivariable*	
	n	*% pre-mature*	OR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
PSD						
Monotherapy	2552	16.9	1.00		1.00	
Dual therapy	958	13.9	0.79 (0.64-0.98)	0.029	0.74 (0.54-1.02)	0.067
HAART, non-PI	788	15.5	0.90 (0.72-1.12)	0.340	0.89 (0.61-1.31)	0.566
HAART, PI	1802	17.3	1.03 (0.88-1.21)	0.739	0.93 (0.67-1.29)	0.665
ECS						
Monotherapy	703	11.7	1.00		1.00	
Dual therapy	294	10.5	0.89 (0.58-1.38)	0.611	0.80 (0.36-1.76)	0.573
HAART, non-PI	591	18.1	1.67 (1.23-2.29)	0.001	2.77 (1.38-5.56)	0.004
HAART, PI	908	17.1	1.56 (1.17-2.08)	0.003	3.04 (1.51-6.13)	0.002
NSHPC						
Monotherapy	957	10.2	1.00		1.00	
Dual therapy	181	8.8	0.85 (0.49-1.48)	0.565	0.55 (0.24-1.29)	0.168
HAART, non-PI	2244	12.8	1.29 (1.01-1.64)	0.043	1.43 (1.02-2.02)	0.039
HAART, PI	2418	12.8	1.28 (1.01-1.63)	0.042	1.51 (1.08-2.11)	0.017

*AORs in the PSD adjusted for maternal ethnicity, region of birth, IDU, symptoms and year of delivery; in the ECS for IDU, CD4 count, site and mother; and in the NSHPC for IDU, symptoms, CD4 count, and mother.

Summary estimates

ECS and NSHPC

Due to heterogeneity between the studies, it was not appropriate to calculate an overall summary estimate for the association between HAART and prematurity in relation to monotherapy. However, as there was no evidence of heterogeneity between the ECS and the NSHPC (χ^2=1.58, df=1, p=0.209), these two studies were combined. Only statistically significant variables that were available in both studies were included. The overall OR for HAART-associated prematurity compared with a baseline of monotherapy was 1.41 (95% CI: 1.19-1.68, p<0.001, n=8305) adjusting only for study, 1.47 (95% CI: 1.23-1.76, p<0.001, n=8269) adjusting for IDU and CD4 cell count as well as study, and 1.36 (95% CI: 1.07-1.72, p=0.011, n=6305) adjusting also for $\log_{10}$ viral load.

Dual therapy baseline

Since there was no significant evidence of heterogeneity between the studies when dual therapy was selected as a reference group (see page 188), a pooled estimate for the association between HAART and prematurity was obtained by combining the three studies. For this analysis, variables had to be consistent across the studies; maternal ethnic group was therefore classified as white, black or other (including Hispanic); and in order to adjust for maternal clinical status, CD4 cell count was used as a proxy for symptoms in the ECS (women with CD4 <200 cells/µl were classified as symptomatic). Three models were developed (Table 5.24): the first was adjusted only for study (model 1); the second also for ethnic group, region of birth, IDU, and year of delivery, but not clinical status due to the high proportion of women with

missing information on this variable (model 2); the third also for clinical status (model 3).

HAART was strongly associated with premature delivery in all three models (Table 5.24); in the final model (model 3), HAART was associated with a 1.5-fold increased risk of prematurity compared with dual therapy, after adjusting for study, ethnic group, region of birth, IDU, clinical status and year. Monotherapy was associated with a small but significant increase in prematurity (OR=1.22, p=0.026) compared with dual therapy in the first model (adjusted only for study), but the effect was reduced and non-significant in the adjusted models.

Study was significantly associated with prematurity in the first model, reflecting the lower baseline prematurity rates in the ECS and NSHPC, compared with the PSD; after adjusting for the other variables, this association was reduced, suggesting that baseline differences in prematurity between the studies were partly explained by these other factors. Although only borderline significant, prematurity remained slightly lower in the NSHPC compared with the PSD, but the differences between the ECS and PSD disappeared.

IDU and clinical status were both strongly associated with prematurity, with AORs around 1.8-1.9. Being born abroad was associated with a significantly lower risk of prematurity (final model, AOR=0.71). Although region of birth was not significant in the ECS or NSHPC models presented earlier (Table 5.18), the AORs were consistent with those for the PSD, and there was no evidence of interaction between study and region of birth (Mantel-Haenszel test for homogeneity of ORs, p=0.579).

Homogeneity tests on unadjusted stratified ORs indicated no evidence of interaction between study and region of birth, IDU or symptoms; there was, however interaction

between study and both ethnic group and year, consistent with earlier results. Excluding these two variables from the final model did not substantially alter the results (data not shown).

Table 5.24 Summary adjusted odds ratios for the association between HAART and prematurity compared with dual therapy

	Model 1 (*n*=14,406)			Model 2 (*n*=13,096)			Model 3 (*n*=10,110)		
	AOR	**(95% CI)**	***p*-value**	**AOR**	**(95% CI)**	***p*-value**	**AOR**	**(95% CI)**	***p*-value**
ART									
Monotherapy	1.22	(1.02-1.46)	0.026	1.17	(0.96-1.42)	0.129	1.13	(0.89-1.43)	0.319
Dual therapy	1.00			1.00			1.00		
HAART	1.41	(1.19-1.68)	<0.001	1.44	(1.19-1.73)	<0.001	1.50	(1.20-1.88)	<0.001
Study									
PSD	1.00			1.00			1.00		
ECS	0.87	(0.77-1.00)	0.042	0.94	(0.78-1.13)	0.508	0.93	(0.75-1.16)	0.529
NSHPC	0.66	(0.59-0.74)	<0.001	0.79	(0.66-0.95)	0.012	0.81	(0.66-1.01)	0.057
Ethnic origin									
White				1.00			1.00		
Black				1.32	(1.10-1.58)	0.002	1.48	(1.20-1.82)	<0.001
Other/Hispanic				1.10	(0.88-1.37)	0.397	1.17	(0.92-1.50)	0.205
Region of birth									
In study region				1.00			1.00		
Abroad				0.73	(0.62-0.86)	<0.001	0.71	(0.59-0.86)	<0.001
IDU									
Non-IDU				1.00			1.00		
IDU				1.85	(1.57-2.18)	<0.001	1.93	(1.59-2.33)	<0.001
Year									
Per year				1.00	(0.98-1.03)	0.686	1.01	(0.98-1.04)	0.476
Clinical status									
Asymptomatic/CD4≥200							1.00		
Symptomatic/CD4<200							1.82	(1.54-2.16)	<0.001

Model 1 adjusted only for study, model 2 for all other variables except symptoms/CD4, and model 3 adjusted also for symptoms/CD4.

Conclusions

There were significant differences between the PSD, ECS and NSHPC in the association between ART and prematurity; in the ECS and NSHPC, HAART was associated with a significantly increased risk of prematurity compared with monotherapy, whereas no such association was observed in the PSD. These differences remained when controlling for other prematurity risk factors, some of which were consistently associated with prematurity (IDU, symptoms, CD4 count), and were also apparent when a lower gestational age (32 weeks) was used as a cut-off. Both PI- and non-PI-based HAART were significantly associated with prematurity in the ECS and NSHPC. The heterogeneity between studies was also not explained by adjusting for random effects attributable to study sites. However, it was not possible to control for some factors in the PSD, including maternal CD4 cell count and repeat pregnancies, both of which had significant effects on the HAART-prematurity association in the other two studies; it is possible that the difference in prematurity between HAART and monotherapy could be due to the inability to adjust for these factors in the PSD.

In all three studies, the risk of prematurity was higher in women on HAART than in those on dual therapy. In a pooled analysis, HAART was associated with a 1.5-fold increased risk of prematurity compared with dual therapy, after adjusting for study, ethnic group, region of birth, IDU, year and clinical status or CD4 count.

In conclusion, pooling data from these three studies revealed a statistically significant association between HAART and prematurity compared with dual therapy, but there was heterogeneity between studies when monotherapy was chosen

as a baseline, which could not clearly be explained by methodology or study-specific factors on which information was available.

5.4 Key Points

Prematurity in the NSHPC

- In the NSHPC, HAART was associated with a 1.6-fold increased risk of premature delivery, compared with mono/dual therapy, which remained after adjusting for clinical status, injecting drug use, ethnic origin and maternal age.
- Low CD4 cell count and high viral load were also independently associated with an increase in prematurity, and adjusting for these factors did not explain the differences observed by type of ART.
- The association between HAART and prematurity was stronger for earlier gestational ages, with over a 2.5-fold increased risk of delivery at <35 or <32 weeks gestation.
- Among women on HAART, prematurity rates did not differ by class of drugs (PIs and/or NNRTIs).
- Later initiation of HAART was associated with significantly reduced prematurity rates. After excluding women who started HAART after 26 weeks to avoid possible selection bias, later initiation was associated with a 10% reduction in prematurity per week of gestation without HAART.
- Findings were robust across different subgroups, including pregnancies in parous and nulliparous women, those before and after 2000, and after excluding stillbirths, dual therapy exposures and ART early in pregnancy.
- Infants exposed to HAART were slightly but significantly lighter for their gestational age, compared with those exposed to monotherapy.

Comparative analysis

- There were substantial differences between the PSD, ECS and NSHPC in the distribution of births over time, maternal characteristics, uptake of interventions, and baseline prematurity rates.
- There were differences in use of ART between studies, overall and within different time periods.
- IDU and maternal clinical and immunological factors (symptoms, CD4 cell count and viral load) were consistently associated with prematurity in the three studies, but maternal ethnic origin and year of delivery were only independently associated with prematurity in the PSD.
- ART was significantly associated with prematurity in all three studies; compared with monotherapy, dual therapy was associated with lower prematurity rates in the PSD, whereas HAART was associated with increased prematurity rates in the ECS and NSHPC.
- With monotherapy as a baseline, there was significant heterogeneity between the studies in the association between HAART and prematurity, and it was therefore not appropriate to pool the studies for this comparison.
- Population characteristics did not explain the differences in the HAART-prematurity relationship; adjusting for IDU, ethnic group, year of delivery, and clinical and immunological factors did not substantially alter the association between treatment and prematurity, and did not remove the differences between studies.

- Heterogeneity between studies remained in analyses involving type of HAART (PI or other) and a prematurity cut-off of <32 weeks, and after adjusting for study site and repeat pregnancies.
- There was no significant heterogeneity between studies with dual therapy as a baseline, and pooling the data from the three studies revealed an overall 1.5-fold increased risk of prematurity associated with HAART, after adjusting for other risk factors.

Chapter 6 Modelling the risks and benefits of antiretroviral therapy in terms of pregnancy outcomes and mother-to-child transmission

There are clear benefits of antiretroviral therapy (ART) in terms of preventing mother-to-child transmission (MTCT), with transmission rates in 2000-2006 around 1% in women on highly active antiretroviral therapy (HAART) (Chapter 3). Nevertheless, there is increasing evidence linking HAART to adverse pregnancy outcomes. In this thesis, significant associations have been shown between HAART and both stillbirth (Chapter 4) and prematurity (Chapter 5). Early HAART was also associated with an increased risk of pre-eclampsia compared with HAART later in pregnancy, although this was only borderline significant (Chapter 4). The aim of this chapter is to model these risks in relation to the reduction in MTCT rates using Monte Carlo simulation methods.

6.1 Methods

Risk and benefit estimates

Since pre-eclampsia in the mother affects the infant mainly by increasing the risk of prematurity and low birth weight (Sibai, Dekker, & Kupferminc, 2005), it was not addressed as a separate outcome in the analyses; risks and benefits were constrained to those directly affecting paediatric outcome. Risk estimates for stillbirth were obtained from the models presented in Chapter 4 (page 116), and estimates for

prematurity were obtained from Chapter 5 (Tables 5.14, page 186; Table 5.21, page 202; and Table 5.22, page 204), and are summarised in Table 6.1 in this Chapter. MTCT rates were derived specifically for these analyses, as appropriate comparisons were not previously shown. In recent years, monotherapy has been recommended only for women not needing HAART for their own health, and the transmission rate in this group is low. In order to obtain an estimate corresponding to a situation where monotherapy is used exclusively, HAART at any time (1990-2006) was compared with monotherapy up to 1997 (by 1998 over a third of women were on HAART; Figure 3.3, page 83).

For the baseline scenario, observed prematurity and MTCT rates in women on monotherapy were used. To estimate adjusted rates in the HAART group, the definition of an odds ratio (OR) was used: $OR = \frac{p_1 / (1 - p_1)}{p_0 / (1 - p_0)}$, where p_0 is the rate in the unexposed or baseline group (i.e. monotherapy), and p_1 is the rate in the exposed group (i.e. HAART) (Kirkwood & Sterne, 2003). Since p_0 and OR were known, the equation could be solved for p_1 to give prematurity and transmission rates for the HAART group:

$$p_1 = \frac{OR \times p_0}{1 - p_0 + (OR \times p_0)} \qquad \text{Equation 1}$$

In order to account for confounding, rates for women on HAART were calculated using adjusted odds ratios (AORs) estimated in logistic regression models.

Incremental risk-benefit ratio

Incremental risks and benefits were calculated as $p_1 - p_0$ (rate in HAART-exposed women minus rate in monotherapy-exposed women); $R_1 - R_0$ was denoted as

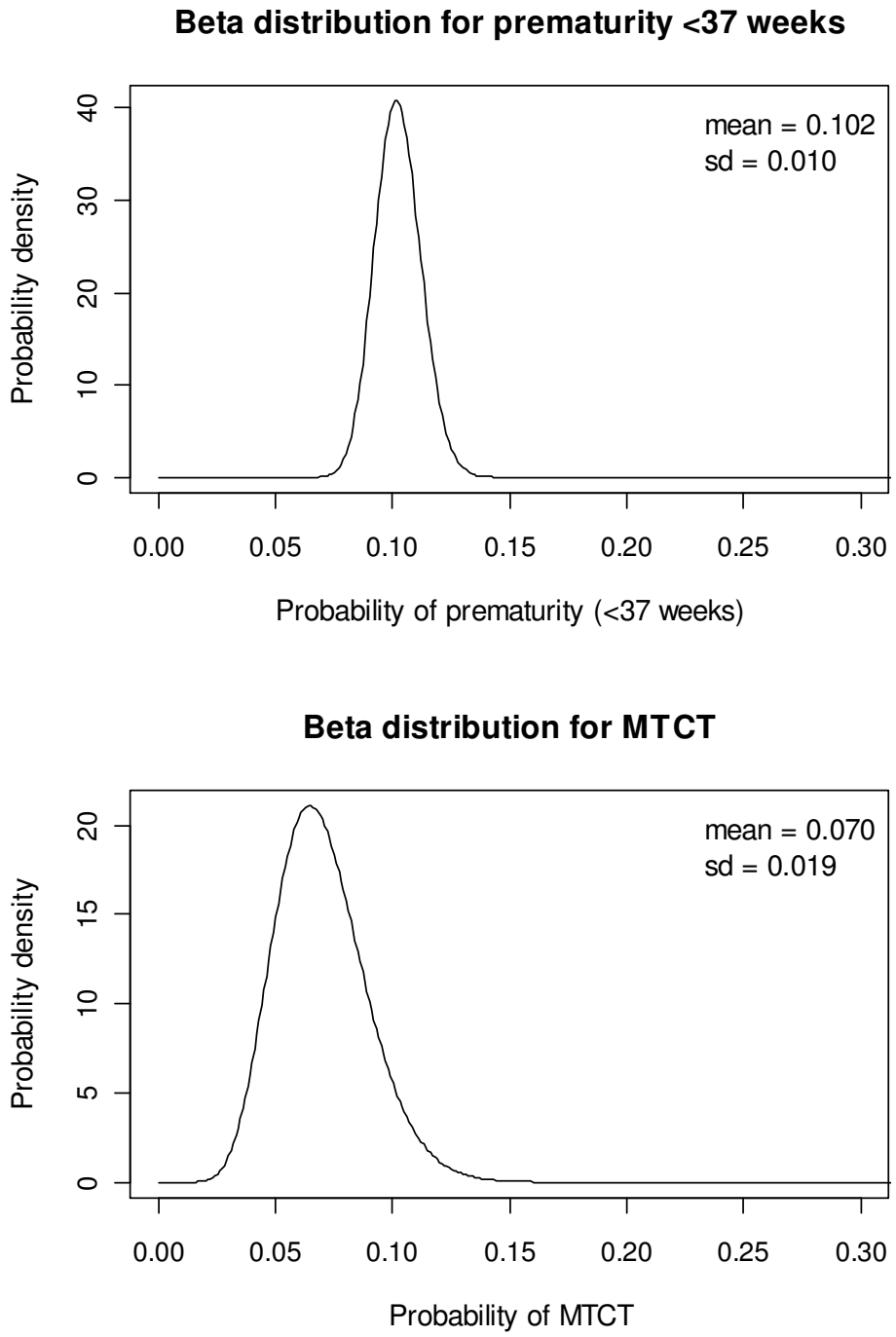
incremental risks and $B_1 - B_0$ as incremental benefits. The incremental risk-benefit ratio (IRBR) is defined as:

$$IRBR = \frac{\Delta R}{\Delta B} = \frac{R_1 - R_0}{B_1 - B_0} \qquad \text{Equation 2}$$

Monte Carlo simulation

In order to incorporate simultaneously the uncertainty from the risk and benefit estimates, Monte Carlo methods suggested by Lynd and O'Brien (Lynd & O'Brien, 2004) were used to simulate the joint probability densities of incremental benefit (MTCT) and incremental risk (prematurity <37 or <32 weeks, or stillbirth). Values for proportions were generated from beta probability density functions (Gupta & Nadarajah, 2004), in order to account for the fact that normality cannot always be assumed when calculating confidence intervals around proportions, which are bounded by the interval [0,1] (Lynd & O'Brien, 2004). A brief explanation of beta distributions is provided in Appendix 5, and the beta distributions modelling the probabilities of prematurity (<37 weeks) and MTCT are shown in Figure 6.1. To model the uncertainty relating to the AOR, the estimate of the natural logarithm of the AOR (ln(AOR)) was used, since it has better statistical properties than the AOR (Kirkwood & Sterne, 2003).

Figure 6.1 Beta distributions describing the probability of prematurity and mother-to-child transmission (MTCT) in women on monotherapy



MTCT, mother-to-child transmission; sd, standard deviation.

The simulations consisted of repeatedly sampling from the assumed parameters' distributions by randomly selecting values from the beta distributions for the baseline proportions and from the normal distributions for ln(AOR), using the following algorithm:

1. A value for the baseline risk ($\hat{R}_0$, denoting sampled R_0) was sampled from the distribution (prematurity or stillbirth) for monotherapy-exposed women, and a value for the baseline MTCT rate ($\hat{B}_0$) was sampled from the MTCT distribution for monotherapy-exposed women (Figure 6.2). This was replicated 1000 times in order to simulate the joint uncertainty around the estimates.

2. ln(AOR)s for the risks and benefits were also randomly sampled 1000 times from the normal distribution, and rates for the HAART group ($\hat{R}_1$ and $\hat{B}_1$) were calculated from Equation 1 using the point estimates for risk and benefit rates in the baseline group (R_0 and B_0), and the sampled ln(AOR).

3. For each of the 1000 realisations, the incremental risk ($\hat{R}_1 - \hat{R}_0$) and incremental benefit ($\hat{B}_1 - \hat{B}_0$) were calculated by subtracting the baseline rate from the adjusted rate.

4. The incremental risk-benefit ratio was then calculated for each risk-benefit pair.

So that simulations could be replicated, the same random number seed was fixed at the start of each simulation using the function '`set.seed`' in R version 2.8.0. The functions '`rbeta`' and '`rnorm`' in R were used to generate values from the beta and normal distributions (R Development Core Team, 2006).

Confidence intervals

Calculating confidence intervals for the IRBR is problematic, since ratios can be negative and tend not to be normally distributed (Briggs, O'Brien, & Blackhouse, 2002). For comparison, four different methods were used to calculate confidence intervals:

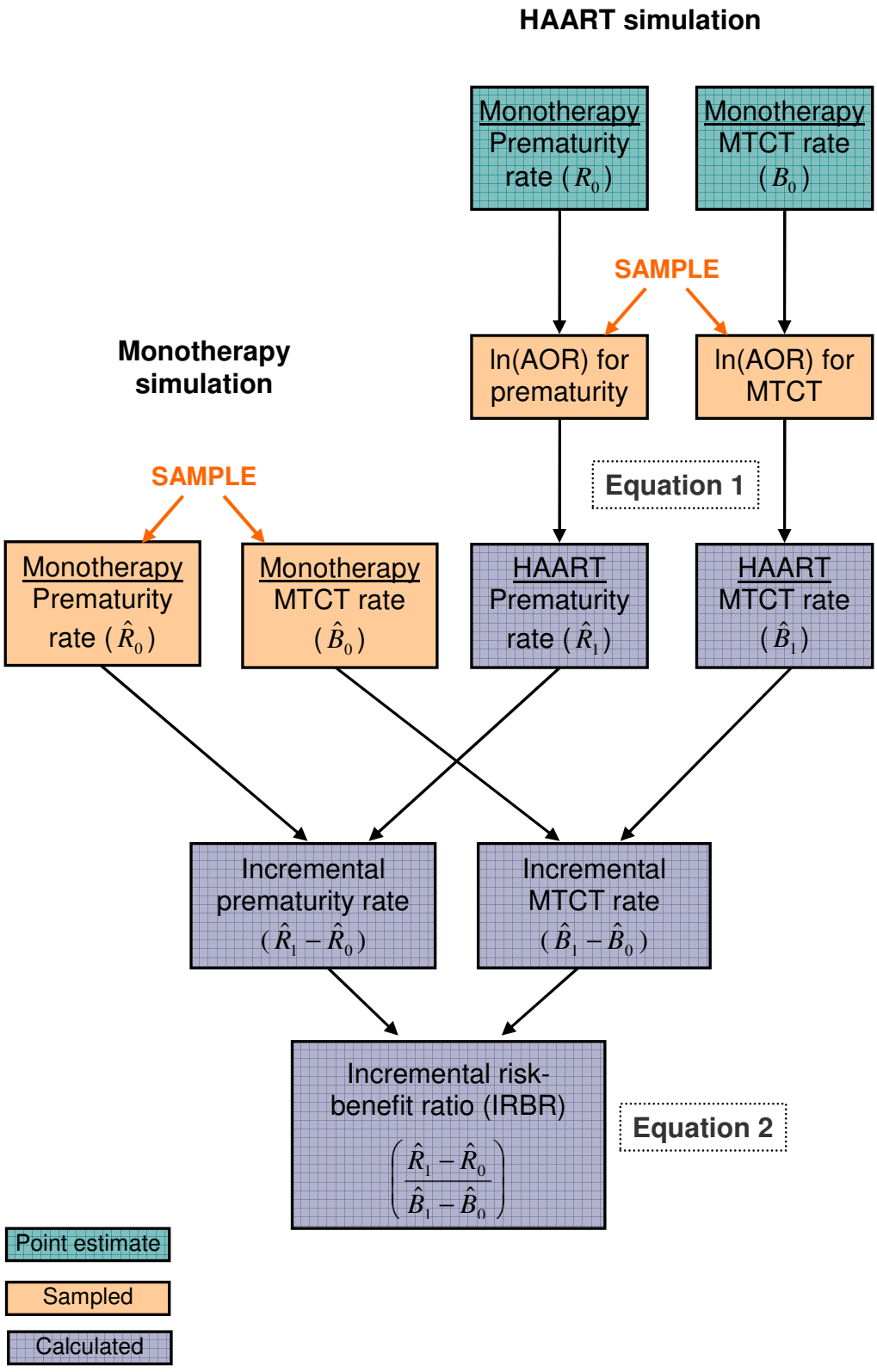
(1) Crude extrapolation from the point estimates for the baseline rates and the confidence intervals around the AORs.

(2) Calculation of the best and worst case scenarios using the confidence intervals around both the baseline and the comparison rates. The lower confidence limit corresponds to the ratio of lowest risk to highest benefit, and the upper interval to the ratio of highest risk to lowest benefit.

(3) The confidence box approach (Briggs, Mooney, & Wonderling, 1999), which involves plotting the confidence intervals for the risk and benefit differences around the point estimate on the risk-benefit plane. These intervals define a box, and the slopes of the two rays which bound the box can be taken as confidence limits for the ratio.

(4) Taking the 2.5% and 97.5% quantiles of the data generated by Monte Carlo simulation.

Figure 6.2 Flowchart showing the simulation algorithm for the Monte Carlo risk-benefit model of ART in pregnancy



HAART, highly active antiretroviral therapy; MTCT, mother-to-child transmission; ln(AOR), natural logarithm of the adjusted odds ratio.

Selective monotherapy scenario

In the basic model, two scenarios were compared: exclusive HAART and exclusive monotherapy. In the UK, zidovudine monotherapy is one of the treatment options for women who do not need HAART for their own health and have a baseline viral load <6000-10,000 copies/ml, if they are willing to deliver by elective caesarean section (BHIVA/CHIVA, 2008). The MTCT rate among the 12% of women on monotherapy between 2000 and 2006 was 0.5% (3/638, 95% CI: 0.1-1.4%), and 73% delivered by elective caesarean section (Chapter 3). This scenario was modelled by sampling 12% of the simulated values (the same proportion as were on monotherapy in 2000-2006) from the monotherapy distributions and the remainder from the HAART distributions; this scenario was compared with the exclusive HAART scenario.

Assumptions and sensitivity analysis

Assumptions

The only risks included in the analysis were ones that were explored in this thesis and directly affected outcomes in the child. Maternal toxicities and adverse events were excluded, as were other paediatric outcomes such as mitochondrial toxicity or anaemia, which could not be assessed through the National Study of HIV in Pregnancy and Childhood (NSHPC). Other benefits of treatment, for instance slowing maternal disease progression, were omitted for the same reasons.

Differences in risks and benefits between the HAART and early (pre-HAART) monotherapy groups were considered to be attributable to the treatment only. No allowance was made for ART duration or indication for treatment (whether HAART was taken for maternal treatment or primarily to prevent MTCT). Although AORs

were used to control for other potential risk factors, baseline rates assumed a prevalence of other risk factors equivalent to the prevalence in this population (described in Chapters 3 and 5).

Association between MTCT and prematurity

Although some studies have shown an increased risk of transmission in infants born prematurely, preterm delivery appears to have reduced importance as a risk factor for MTCT in treated women. This could be a consequence of a differential effect of prematurity by viral load or mode of delivery, or because of reduced statistical power, given the small number of transmissions in treated women. Prematurity was not an independent risk factor for MTCT in this population (as reported in Chapter 3), and the association observed in the unadjusted analysis was mainly a result of reduced maternal exposure to ART and unplanned vaginal delivery, both commonly associated with premature delivery. Furthermore, prematurity was not a significant risk factor for MTCT in women on HAART.

However, the effect of an association between prematurity and MTCT was investigated in a sensitivity analysis. Models were adapted by incorporating a relative risk for the increase in MTCT resulting from premature delivery. For each simulation, a transmission rate ($\hat{B}_0$) was generated from a beta distribution; the corresponding transmission rates for premature and term infants were then derived using the equations shown in Appendix 6. A sampled prematurity rate was then realised ($\hat{R}_0$), and the sampled transmission rate was adjusted by taking the weighted average of the transmission rates in the term and premature groups (Equation 5, Appendix 6).

6.2 Prematurity and mother-to-child transmission

Risk and benefit estimates

The estimates used in the risk-benefit models are shown in Table 6.1. For prematurity, estimates were obtained from Chapter 5. For MTCT, rates in women on HAART were compared with those in women on monotherapy before HAART became available in 1998. Results of this comparison are shown in Table 6.2. HAART was associated with an 87% reduction in MTCT compared with pre-1998 monotherapy (AOR=0.13). Although the transmission rate in this analysis was higher in very premature infants than in term infants (6.7% versus 2.7%), there was no significant association after adjusting for ART, mode of delivery and sex (AOR=1.14, p=0.86).

Table 6.1 Prematurity and mother-to-child transmission estimates

	Estimate	*n*	SE	(95% CI)	From
Prematurity <37 weeks					
Baseline rate, mono *(R_0)*	10.2%	98/957	0.010	(8.4-12.3)	Table 5.14, p. 186
AOR (HAART vs. mono)	1.47		0.237	(1.07-2.02)	Table 5.21, p. 202*
Prematurity <32 weeks					
Baseline rate, mono *(R_0)*	1.4%	13/957	0.004	(0.7-2.3)	Table 5.22, p. 204
AOR (HAART vs. mono)	2.06		0.666	(1.09-3.88)	Table 5.22, p. 204
Stillbirth					
Baseline rate, mono *(R_0)*	0.3%	3/1061	0.002	(0.06-0.82)	Table 4.2, p. 117
AOR (HAART vs. mono)	3.10		1.854	(0.98-10.0)	Chapter 4, p. 116
Mother-to-child transmission					
Baseline rate, mono *(B_0)*	7.0%	12/172	0.019	(3.7-11.9)	Table 6.2
AOR (HAART vs. mono)	0.13		0.048	(0.06-0.27)	Table 6.2

SE, standard error.
* Estimates were taken from Section 5.2, rather than Section 5.1, because stillbirth and prematurity are analysed as a separate outcomes in this chapter, and prematurity estimates in Section 5.2 excluded stillbirths. Furthermore, the analysis in Section 5.2 was based on a later (and larger) dataset.

Table 6.2 Rates and adjusted odds ratios for mother-to-child transmission, comparing HAART (anytime) with monotherapy in the pre-HAART era (before 1998)

	n	Infected		Multivariable model (*n* =4319)			
	(total)	*n*	%	*n*	AOR	95% CI	*p-value*
Antiretroviral therapy							
Monotherapy (pre-1998)	172	12	7.0	148	1.00		
HAART	4282	42	1.0	4171	0.13	(0.06-0.27)	<0.001
Mode of delivery							
Elective caesarean section	3263	31	1.0	2398	1.00		
Emergency caesarean section	1126	21	1.9	902	2.34	(1.12-4.88)	0.024
Vaginal delivery	1310	49	3.7	1019	1.51	(0.76-2.98)	0.238
Gestational age							
≥37 weeks	5230	140	2.7	3772	1.00		
35-36 weeks	373	10	2.7	271	0.69	(0.21-2.35)	0.557
32-34 weeks	220	7	3.2	171	1.50	(0.49-4.55)	0.478
<32 weeks	135	9	6.7	105	1.14	(0.26-5.08)	0.860
Sex of infant							
Male	3091	69	2.2	2155	1.00		
Female	3019	99	3.3	2164	2.31	(1.27-4.18)	0.006

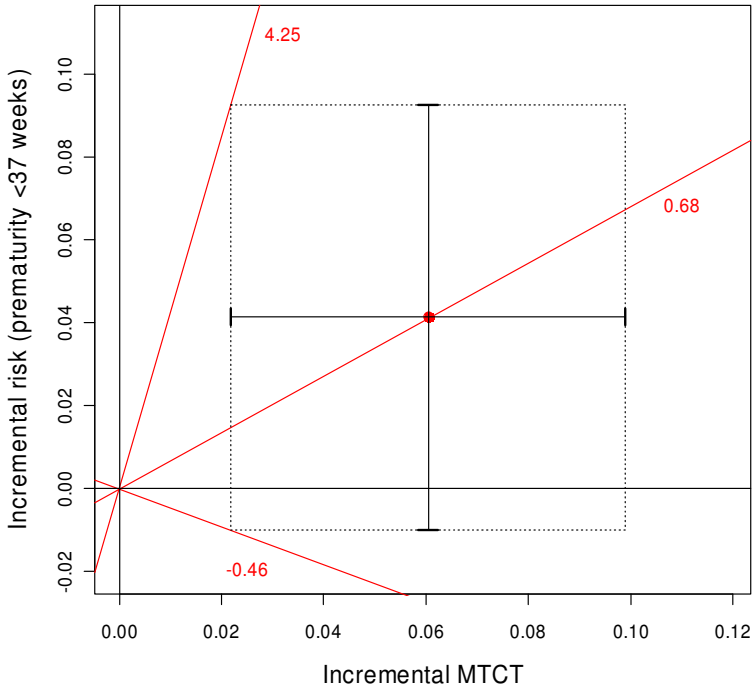
* Estimates were obtained from a similar dataset used in the MTCT analyses in Chapter 3, but with the exclusion of births to women on monotherapy since 2000 (*n*=638), and the addition of births to women on monotherapy before 1998 (*n*=172) or HAART before 2000 (*n*=162).

Point estimates for the incremental risk-benefit ratio

The incremental benefit associated with exclusive HAART (versus exclusive monotherapy) was a reduction in MTCT of 6.0%, and the incremental risk was an increase in prematurity of 4.1% for <37 weeks and 1.4% for <32 weeks. The incremental risk-benefit ratio (from Equation 2) was 0.68 premature infants and 0.23 very premature infants for each infection averted.

One way of crudely displaying confidence limits for the incremental risks and benefits is shown in Figure 6.3, with the horizontal bar corresponding to the confidence interval for the incremental MTCT benefits (0.10%, 2.2%), and the vertical bar to the confidence interval for the incremental prematurity risk (-0.01%, 9.3%). The two bars intersect at the point (ΔB, ΔR) and the slope of the line passing through that point is therefore equal to $\Delta B/\Delta R$ or the incremental risk-benefit ratio. The 'confidence box' resulting from the two bars can be drawn, and corresponds to the combined area of confidence (Briggs, Mooney, & Wonderling, 1999). The slopes of the lines that intersect with the corners of the box can be taken as an approximation to the 95% confidence limits (-0.46, 4.25). However, this interval is wider than the true 95% confidence interval for the ratio, because it does not consider the elliptical nature of the joint distribution, which arises from the fact that the chance of falling simultaneously at the edge of the risk and benefit distributions (i.e. in one of the corners of the box) is lower than 5% (Polsky *et al.*, 1997). The confidence box approach also assumes that the incremental risks and benefits are normally distributed, which may not be the case.

Figure 6.3 Risk-benefit plane showing the incremental risks of prematurity and benefits in terms of MTCT, for exclusive HAART compared with exclusive monotherapy, with 95% confidence intervals and resulting confidence box.



Simulation

To avoid the limitations of the confidence box method for obtaining confidence limits, the joint probability densities of prematurity and MTCT were modelled using a two-stage Monte Carlo algorithm (Lynd & O'Brien, 2004) (as shown in Figure 6.2), which does not require any particular distributional assumptions about the incremental risk-benefit ratio. This method simulates the probabilities of prematurity and transmission for women assumed to be treated with either monotherapy or HAART. One thousand simulated risks and benefits for monotherapy (red triangles) and HAART (black circles) are plotted in Figure 6.4. A clear difference between the two treatment groups was apparent; the limited overlap on the horizontal axis reflects the strong and highly significant association between treatment and MTCT, while the overlap between points on the vertical axis reflects the fact that the confidence

interval for the prematurity AOR approaches one. The simulation was repeated for prematurity at <32 weeks, and a similar pattern was observed (Figure 6.5). Note the difference in the *y*-axis' scales for the two Figures.

The incremental risk-benefit pairs were then computed using the simulated rates. The frequency distributions of the simulated ratio estimates for prematurity <37 weeks and <32 weeks are shown in Figures 6.6 and 6.7. The skewed nature of the distributions is one of the reasons for not computing confidence intervals using methods based on the normal distribution. The median value was taken as the estimate for the incremental risk-benefit ratio: 0.69 premature infants and 0.24 very premature infants for each infection averted. While the median values were very close to the point estimates (0.68 and 0.23, respectively), the means tended to be higher (0.81 and 0.30, respectively) due to the right-skewed distribution of the ratios.

Figure 6.4 Joint densities of prematurity and mother-to-child transmission, resulting from 1000 simulations

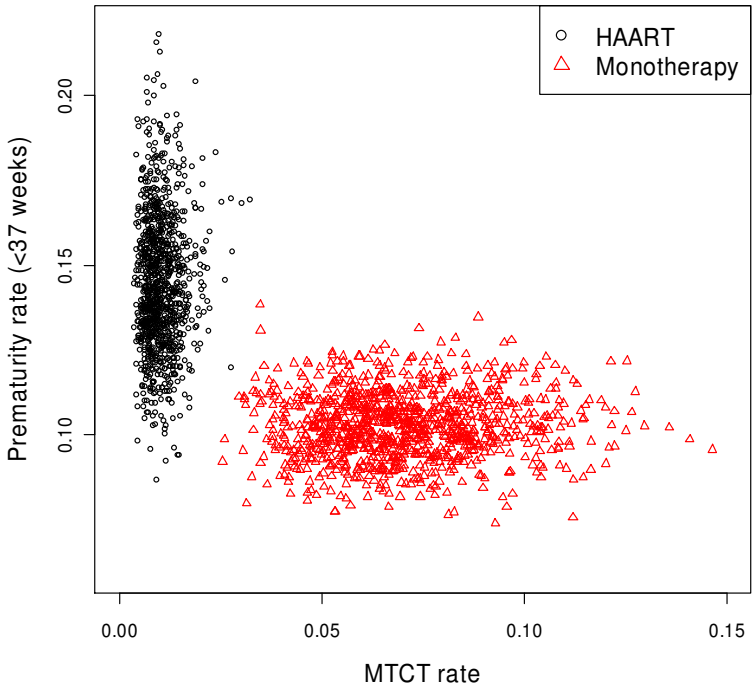
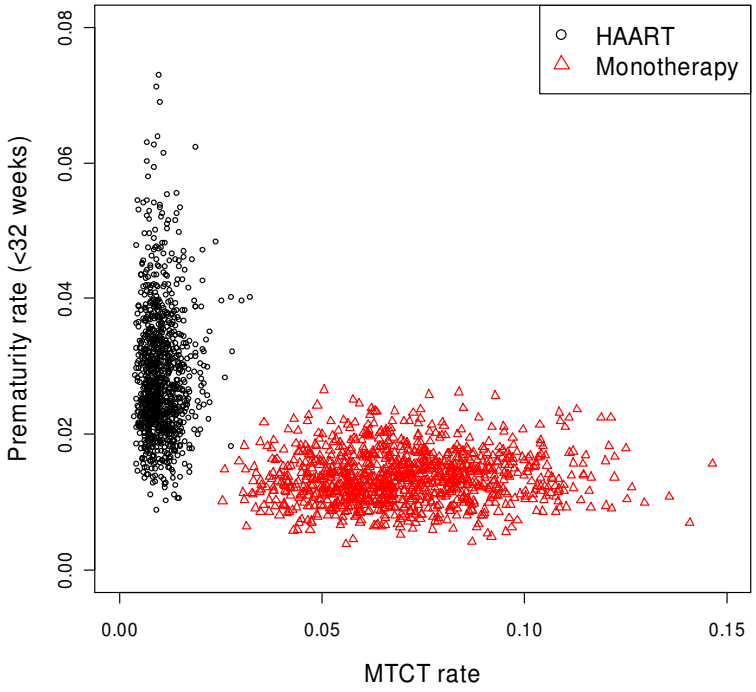


Figure 6.5 Joint densities of severe prematurity (<32 weeks) and mother-to-child transmission, resulting from 1000 simulations



Note: *y*-axis scale differs from Figure 6.4

Figure 6.6 Distribution of 1000 simulations of the incremental risk-benefit ratio estimate for prematurity

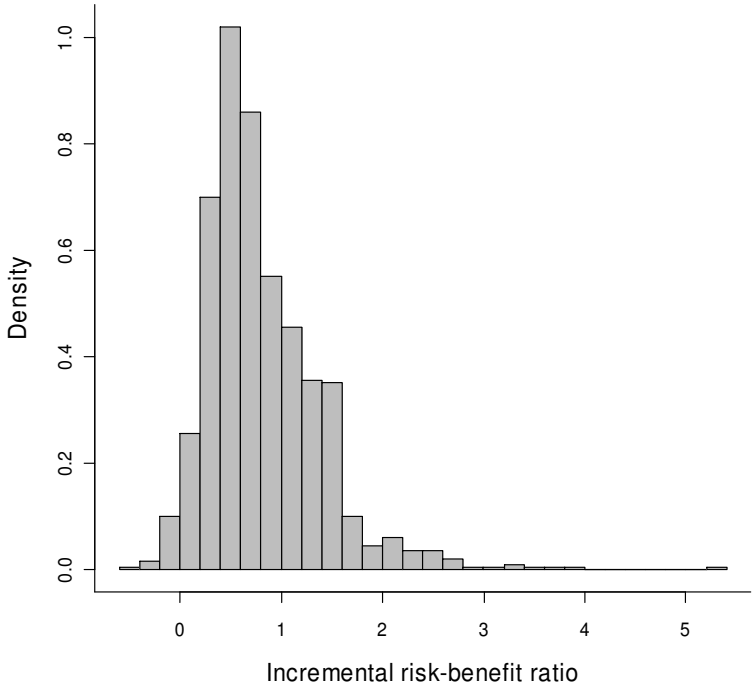
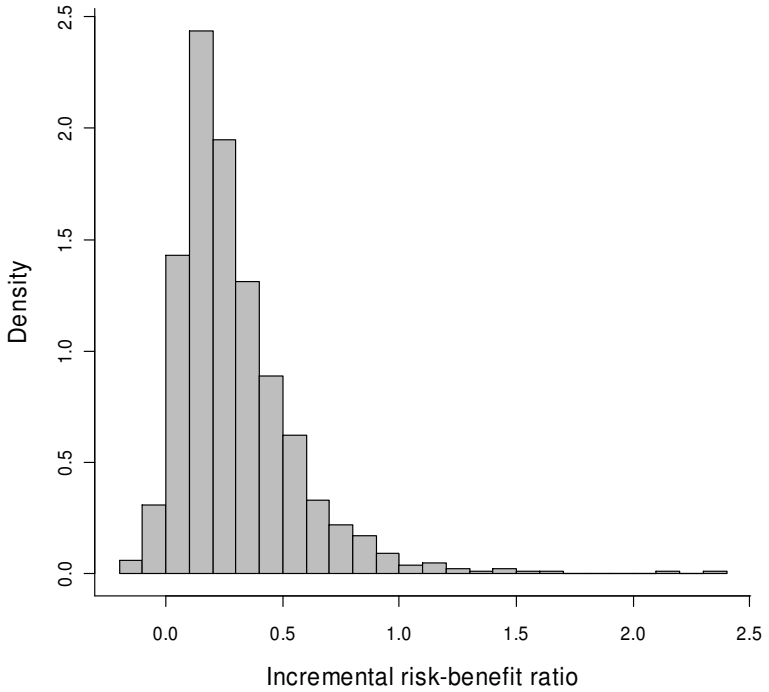


Figure 6.7 Distribution of 1000 simulations of the incremental risk-benefit ratio estimate for severe prematurity (<32 weeks)



Risk-benefit plane

The incremental risk-benefit pairs for the simulations were then plotted on a risk-benefit plane (Figures 6.8 and 6.9), with the *x*-axis representing the difference in the probability of a benefit (a reduction in MTCT) (ΔB) occurring with HAART relative to monotherapy; and the *y*-axis representing the difference in the probability of an adverse event (ΔR) (premature delivery at <37 weeks or <32 weeks).

Risk-benefit acceptability thresholds

The red lines in Figures 6.8 and 6.9 correspond to acceptability thresholds (μ), or the number of adverse events we would be willing to accept for one additional beneficial event. The line μ=1 (shown in blue) means that for one additional transmission averted, we would be willing to accept one additional premature delivery. If we take this to be true, this condition is satisfied for all the points lying below this line, but not for those lying above it. The proportion of points below the line therefore corresponds to the probability that the condition (each beneficial event corresponding to *one* adverse event) is satisfied. These lines can also be used to indicate confidence limits: the upper and lower red lines indicate the limits between which fall 95% of the points, and correspond to μ=0.01 and μ=2.22 in the first model (prematurity <37 weeks), and μ= -0.01 and μ=0.94 in the second model (prematurity <32 weeks).

In the model for prematurity <37 weeks, 95% of the points fell below the line with slope μ=1.75; the corresponding line for the <32 weeks model had a slope of μ=0.77. There is therefore a 95% chance that for each transmission avoided, the maximum number of premature infants (<37 weeks) would be 1.75 and the maximum number of very premature infants (<32 weeks) would be 0.77. This approach can be used instead of a confidence interval.

Figure 6.8 Risk-benefit plane showing the incremental risk of prematurity relative to the incremental MTCT benefit, for exclusive HAART compared with exclusive monotherapy

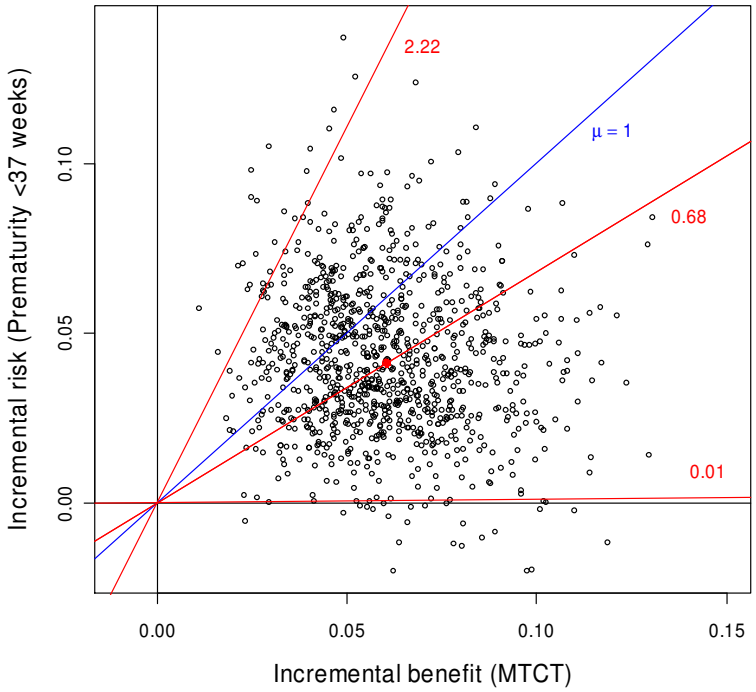
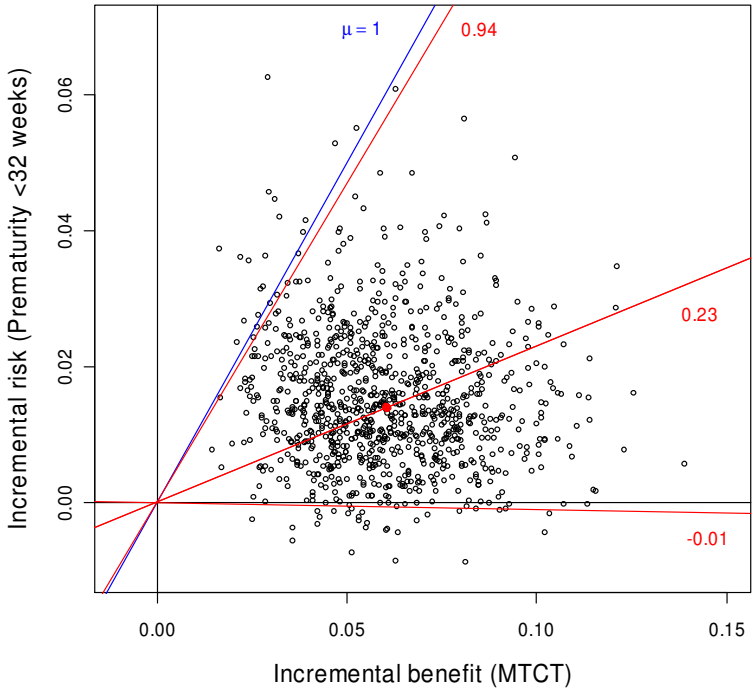


Figure 6.9 Risk-benefit plane showing the incremental risk of severe prematurity (<32 weeks) relative to the incremental MTCT benefit, for exclusive HAART compared with exclusive monotherapy



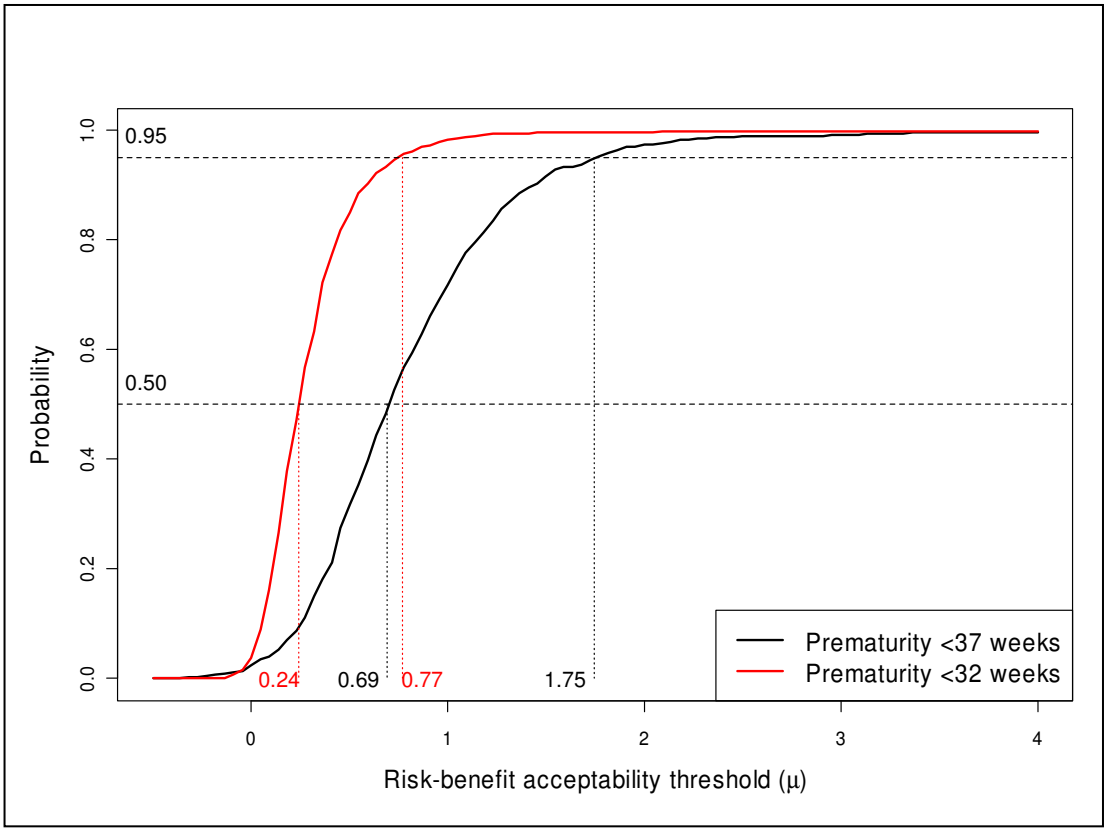
Points correspond to results of 1000 Monte Carlo simulations; lines represent acceptability thresholds (μ), with slope values provided. MTCT, mother-to-child transmission.

Risk-benefit acceptability curve

The risk-benefit acceptability threshold (μ) is not usually a known value; indeed, the number of adverse events one would be willing to accept for a given benefit may vary according to a number of factors, such as the population and the resources available to manage the adverse events in question. In general, a treatment can be considered beneficial if the incremental risk-benefit ratio lies below the chosen value of μ (Lynd & O'Brien, 2004). If μ is not known, its value can be varied, and the proportion of points falling below the line with slope equal to μ can be plotted against the range of possible values of μ (Figure 6.10); this proportion corresponds to an estimate of the probability of the treatment providing a net benefit for a given risk-benefit acceptability threshold. The vertical dotted lines in Figure 6.10 indicate the acceptability thresholds (values of μ) described on page 231, corresponding to the median (point estimate) and the 95% probability level for each of the two models (prematurity <37 weeks and <32 weeks). For example, the risk-benefit acceptability curve for the prematurity <37 model (shown in black) intersects the point (1.75, 0.95), indicating that 95% of the simulated points on the risk-benefit plane fell below the line with slope equal to μ=1.75.

Acceptability thresholds can be decided on the basis of relative morbidity, mortality, cost, or quality of life data; the probability of an overall benefit based on a particular acceptability threshold can then be determined from the risk-benefit acceptability curve. For example, if it were decided that one premature delivery would be considered acceptable in order to avert one transmission (i.e. μ=1), the curve would indicate that (1) this threshold lay above the point estimate for the IRBR (along the *x*-axis), and the treatment should therefore be accepted, and (2) the probability of there being a net benefit at this threshold would be ~70%.

Figure 6.10 Risk-benefit acceptability curve for the probability that HAART provides a net benefit relative to monotherapy at a given risk-benefit acceptability threshold (μ)



Confidence intervals

Confidence limits calculated from the confidence box method and from the simulated data were shown above, and are summarised (for prematurity <37 weeks) in Table 6.3. Confidence intervals can also be calculated crudely by computing upper and lower limits from the baseline estimates and the limits of the confidence intervals for the AOR; this method yields a much narrower interval as it only takes into account the uncertainty in the AOR and not the uncertainty around the estimates of baseline (monotherapy) and comparison (HAART) rates. Alternatively, confidence intervals can be calculated by computing the worst and best case scenarios and calculating a ratio for each (Table 6.3). This method yields a much wider interval than the simulation method, because like the confidence box method it ignores the fact that the probability of falling simultaneously in the tails of the two distributions being compared is less than 5%. The quantile method based on the simulated data provided the best estimate of the confidence interval for the incremental risk-benefit ratio, since it allows for non-normality in the distribution of the ratio, and avoids the obvious limitations of the other three approaches.

Table 6.3 Comparison of alternative methods for estimation of the 95% confidence interval of the incremental risk-benefit ratio for prematurity <37 weeks

Method for calculating confidence interval	Point estimate	95% CI	Range	Limitation
Crude, based on AOR limits	0.68	0.10, 1.69	1.59	Ignores uncertainty around baseline estimates
Confidence box *	0.68	-0.46, 4.25	4.71	Ignores reduced probability of falling simultaneously in tails of two distributions
Best/worst case scenarios **	0.68	-0.13, 6.00	6.13	
Quantiles of simulated data	0.69	0.01, 2.22	2.21	

* Based on a normal approximation for confidence intervals
** Based on exact confidence intervals

Association between prematurity and MTCT

The model was then adapted to incorporate a measure of association between risks and benefits, to allow for the possibility of an increased risk of transmission in infants born prematurely. Because no such association was detected in this population of women reported to the NSHPC, the relative risk of MTCT in the premature group compared with the term group was varied in a sensitivity analysis. The adjustment was fixed so that for a sampled prematurity rate falling on or near the point estimate, the 'adjusted' MTCT rate would remain close to the sampled rate. However, if a higher prematurity rate was sampled, the sampled MTCT rate would be raised due to the increased risk of transmission in the premature proportion, and vice versa. The point estimates therefore remained unchanged whatever the association between prematurity and MTCT. Modelling up to a four-fold increased risk of transmission associated with prematurity produced only a small shift in the joint densities. The confidence intervals remained similar to those in the unadjusted model (see summary findings, Table 6.4, page 244).

6.3 Stillbirth

To model the increased risk of stillbirth associated with HAART (shown in Chapter 4) in relation to the reduction in MTCT, the simulation was repeated with stillbirth as the adverse outcome. Results of the simulations are shown in Figures 6.11 and 6.12. Rates and AORs used in the model are shown in Table 6.1. The incremental risk-benefit ratio was 0.10 additional stillbirths for each infection averted, with 95% of the simulations lying between -0.02 and 0.54. In other words one additional stillbirth would be expected for every 10 averted transmissions. The negative lower quartile (-0.02) reflects the fact that the AOR for the association between HAART and stillbirth (relative to monotherapy) was only borderline significant (p=0.055).

Figure 6.11 Joint densities of stillbirth and mother-to-child transmission, resulting from 1000 simulations

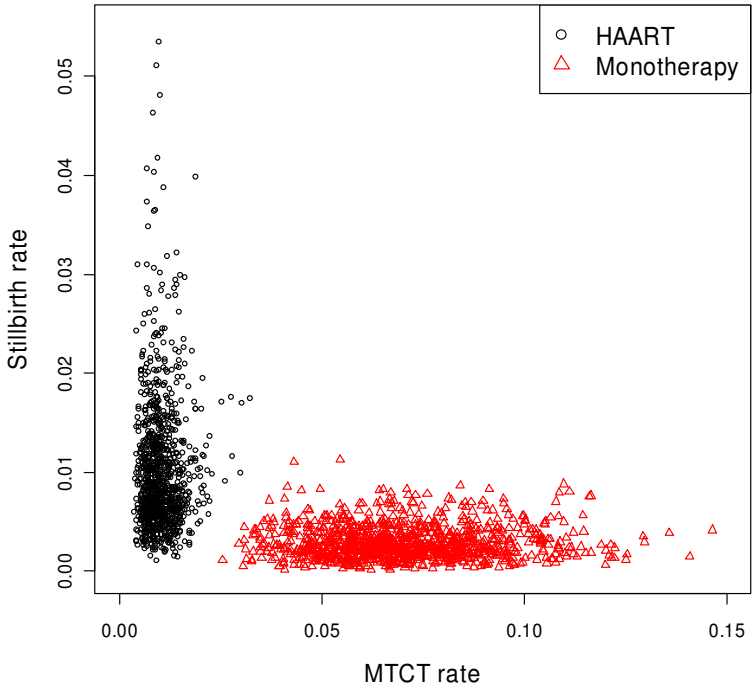
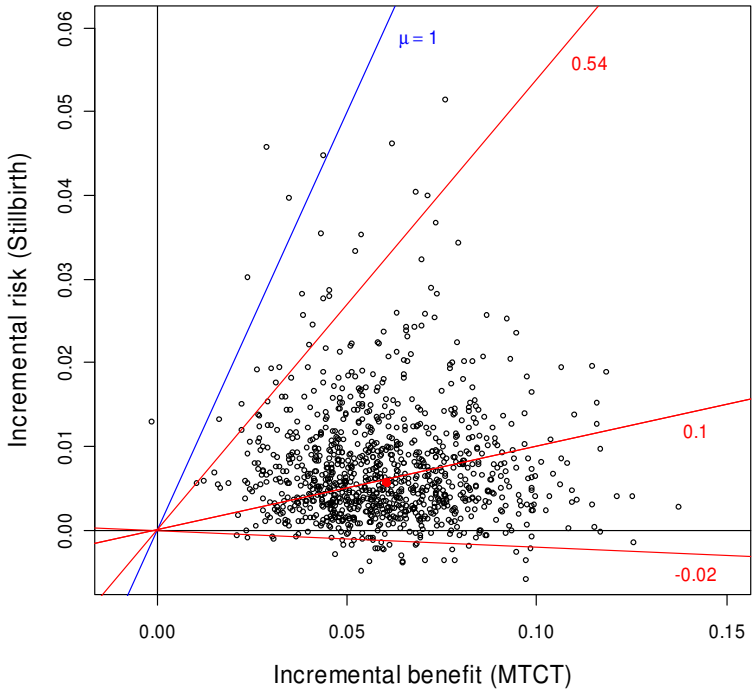


Figure 6.12 Risk-benefit plane showing the incremental risk of stillbirth relative to the incremental MTCT benefit, for exclusive HAART compared with exclusive monotherapy



Points correspond to results of 1000 Monte Carlo simulations; lines represent acceptability thresholds (μ)

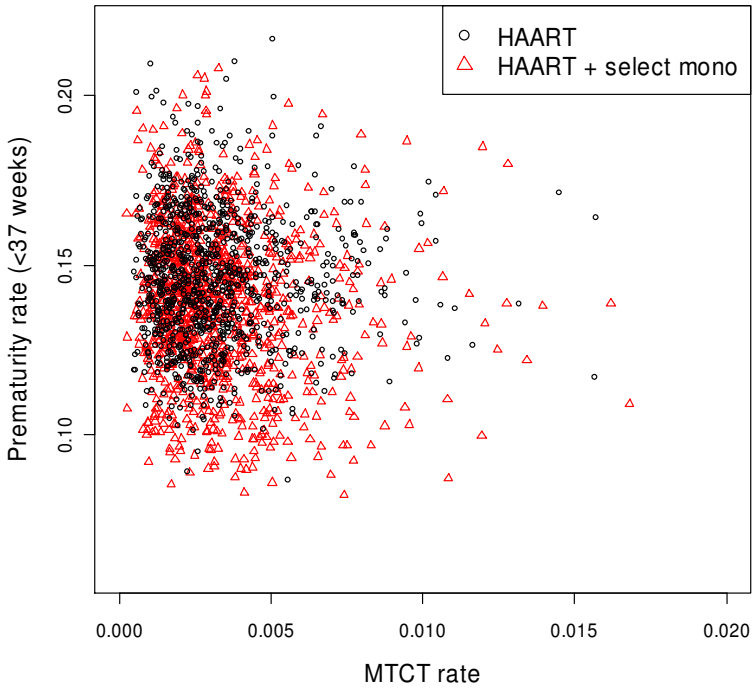
6.4 Selective monotherapy scenario

A scenario representative of recent years, with selective use of monotherapy for healthier women with a low transmission risk (Table 6.1), was then modelled, and the exclusive HAART scenario was compared with the combined scenario. Figure 6.13 shows the joint densities of prematurity (<37 weeks) and MTCT for the HAART scenario (black circles) and the selective monotherapy scenario (red triangles). Although the joint distributions of two scenarios overlap substantially, the lower prematurity rate among women on monotherapy is reflected in the cluster of red triangles around the 10% prematurity level. Incremental risk-benefit pairs are plotted in Figure 6.14. The points cluster around the origin, indicating that there is little difference between the two scenarios. The median point is located at (0, 0.007), indicating no difference in transmission rates, but a small increase in risk associated with the exclusive HAART scenario. This example demonstrates one of the problems of ratio estimation: as the difference in benefit (denominator) approaches zero, the ratio approaches infinity. Indeed, in Figure 6.14, the line intersecting the median point would be vertical and has been omitted. Point estimates and confidence intervals are shown in the summary table (Table 6.4), but do not provide useful information.

At a population level, the combined scenario provides only a small reduction in risk compared with exclusive HAART (since only 12% of the women are subject to different treatments), with no discernable difference in transmission rates. However, this should not be interpreted as evidence against the use of selective monotherapy, because for women who do not require HAART for their own health, HAART is

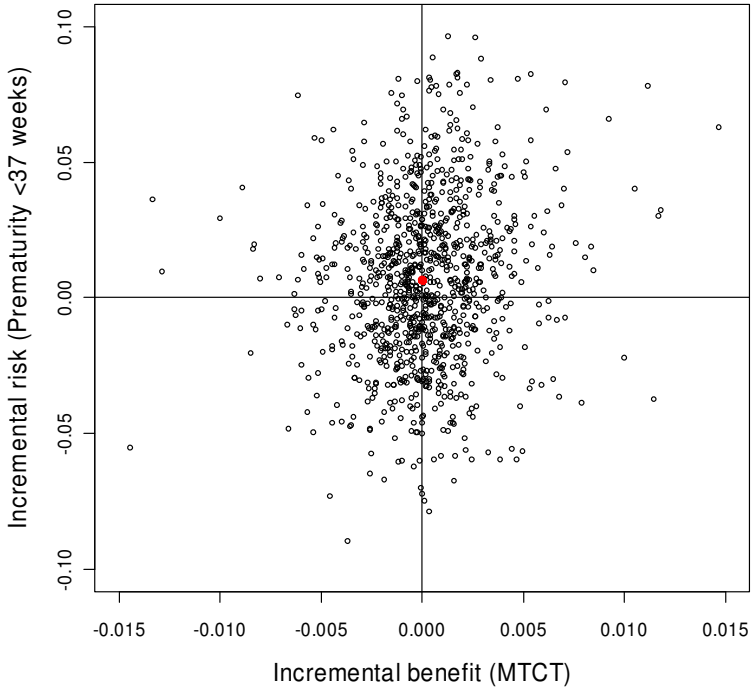
associated with a significantly increased prematurity risk, while not providing any additional benefits in terms of transmission risk, according to the estimates obtained using NSHPC data.

Figure 6.13 Joint densities of prematurity and mother-to-child transmission, resulting from 1000 simulations – exclusive HAART versus combined HAART/selective monotherapy scenario



'HAART + select mono' corresponds to a scenario where 88% of women receive HAART and 12% receive monotherapy

Figure 6.14 Risk-benefit plane showing incremental risks of prematurity and MTCT benefits, for exclusive HAART versus combined HAART/selective monotherapy scenario



6.5 Summary of scenarios

Table 6.4 shows the incremental risk-benefit ratios for prematurity <37 weeks (scenario 1), prematurity <32 weeks (scenario 2) and stillbirth (scenario 3) with exclusive HAART compared with exclusive monotherapy. These findings suggest that avoiding 100 transmissions through exclusive use of HAART would result in an additional 68 infants born at <37 weeks, of whom 23 would be born at <32 weeks, as well as 10 additional stillbirths. The minimal effects of incorporating a two-fold and four-fold increased risk of MTCT associated with prematurity are also shown (scenarios 4 and 5).

Table 6.4 Results of six Monte Carlo simulations of risk and benefits associated with different treatment scenarios

Scenario and parameters		Result	Rates		Incremental rate difference		95% confidence limits (simulation)
			Baseline group	Exclusive HAART	Point estimate	Simulation median	
1	Risk=prem <37 wks, baseline=selective mono, RR=1	*Risk*	10.24	14.37	4.13	4.01	(0.04, 8.9)
		Benefit	6.98	0.94	6.04	5.79	(2.62, 10.59)
		IRBR			0.68	0.69	(0.01, 2.22)
2	Risk=prem <32 wks, baseline=selective mono, RR=1	*Risk*	1.36	2.75	1.40	1.38	(-0.1, 3.98)
		Benefit	6.98	0.94	6.04	5.77	(2.56, 10.25)
		IRBR			0.23	0.24	(-0.01, 0.94)
3	Risk=stillbirth, baseline=selective mono, RR=1	*Risk*	0.28	0.86	0.58	0.59	(-0.14, 2.55)
		Benefit	6.98	0.94	6.04	5.79	(2.61, 10.11)
		IRBR			0.10	0.10	(-0.02, 0.54)
4	Risk=prem <37 wks, baseline=selective mono, RR=2	*Risk*	10.24	14.37	4.13	4.01	(0.04, 8.9)
		Benefit	6.98	0.94	6.04	5.80	(2.64, 10.42)
		IRBR			0.68	0.68	(0.01, 2.22)
5	Risk=prem <37 wks, baseline=selective mono, RR=4	*Risk*	10.24	14.37	4.13	4.01	(0.04, 8.9)
		Benefit	6.98	0.94	6.04	5.79	(2.61, 10.5)
		IRBR			0.68	0.68	(0.01, 2.24)
6	Risk=prem <37 wks, exclusive HAART vs. 12% selective mono, RR=1	*Risk*	13.88	14.37	0.50	0.66	(-5.19, 7.46)
		Benefit	0.81	0.94	-0.13	-0.09	(-1.81, 1.81)
		IRBR			-3.80	-0.33	(-68.47, 52.4)

Prem, prematurity; mono, monotherapy; RR, relative risk of transmission in premature infants compared with term infants

6.6 Key Points

- Monte Carlo simulation was used to model the joint uncertainty around risks and benefits associated with ART, and estimates of the ratio of risks to benefits were calculated. Confidence intervals for the estimates were obtained by taking quantiles of the simulated data.
- The incremental risk-benefit ratios for prematurity (<37 weeks), severe prematurity (<32 weeks) and stillbirth were 0.68 (95% CI: 0.01, 2.22), 0.23 (-0.01, 0.94), and 0.10 (-0.02, 0.54) adverse events, respectively, for each additional transmission event averted by exclusive use of HAART compared with exclusive monotherapy.
- In a sensitivity analysis enabling an increase in transmission among premature infants compared with term infants to be incorporated into the model, even a four-fold increase in MTCT associated with prematurity was shown not to substantially alter the incremental risk-benefit ratio or the confidence intervals.
- In a scenario comparing HAART and selective use of monotherapy with exclusive HAART, little difference was observed at a population level. However, for women who do not require HAART for their own health, monotherapy is associated with a significantly lower risk of prematurity than HAART, with no additional benefits in terms of MTCT.

Chapter 7 Discussion

7.1 HIV in pregnant women in the UK and Ireland

The prevalence of HIV in pregnant women in the UK has increased substantially since the mid-1990s, reaching 0.21% in 2007 in areas of England and Scotland covered by the unlinked anonymous seroprevalence survey (Health Protection Agency, 2008). Since the introduction of effective antiretroviral therapy (ART), an increasing number of diagnosed HIV-infected women have become pregnant, as evidenced by increasing birth rates in infected women (European Collaborative Study, 2005b; Massad *et al.*, 2004). Universal antenatal HIV screening, introduced from 2000 onwards in the UK and Ireland, now ensures that the majority of infected women (over 95%) are diagnosed before they deliver, in time to be offered interventions to reduce the risk of mother-to-child transmission (MTCT) (Health Protection Agency, 2008). The result of these parallel trends has been a dramatic increase in the number of pregnancies in diagnosed HIV-infected women reported to the UK and Ireland national surveillance scheme, the National Study of HIV in Pregnancy and Childhood (NSHPC) (Chapter 3). The annual number of reported pregnancies increased from around 100 in the early 1990s to over 1200 in 2006, the sharpest rise occurring between 1999 and 2003, when uptake of universal screening also rose substantially (Townsend, Cliffe, & Tookey, 2006).

Changes in antenatal screening policies also affected the proportion of women diagnosed before or during pregnancy. Immediately after routine screening was introduced, pregnancies in women diagnosed antenatally surpassed those in women

who were already diagnosed when they became pregnant. This pattern was reversed within five years, as women who were previously diagnosed in an antenatal setting were reported with subsequent pregnancies; over 1200 women included in the surveillance between 1990 and 2006 had more than one pregnancy notified during this period. Although the number of reports continued to rise each year, the rate of increase declined in recent years, possibly because the proportion of HIV-infected women diagnosed by delivery has stabilised at around 95% since 2004 (Figure 1.5, page 31) (The UK Collaborative Group for HIV and STI Surveillance, 2007). However, since the majority of pregnancies in HIV-infected women in the UK and Ireland are in women from sub-Saharan Africa, the number of reports is also likely to be influenced by patterns of migration from Africa. Noticeable trends in country of origin have been reported among HIV-infected Africans seeking HIV care in London, with possible links to periods of conflict within Africa (Forsyth, Burns, & French, 2005; Sinka *et al.*, 2003).

Pregnancy terminations and miscarriages occurring after booking for antenatal care were also reported to the surveillance study, although very early miscarriages and terminations carried out in specialist clinics were likely not reported. Nevertheless, because the overall design of the surveillance study remained constant, as did the inclusion criteria (all pregnancies in diagnosed HIV-infected women seen in antenatal clinics, regardless of timing of diagnosis or pregnancy outcome), these data can provide an indication of trends in these pregnancy outcomes. There was no change over time in the proportion of miscarriages or late miscarriages (after 19 weeks gestation). An overall decline in the proportion of pregnancy terminations was observed in this population, and was probably related to reductions in HIV-associated morbidity and mortality and in mother-to-child transmission rates

following the introduction of ART (Duong *et al.*, 1999; European Collaborative Study, 2005d; Mocroft *et al.*, 2003). The lower termination rate in women diagnosed during pregnancy compared with those diagnosed previously could be due to differential reporting of terminations between the two groups, but could also reflect a lack of opportunity for termination among women diagnosed later in pregnancy, as suggested by the later median gestational age at termination in this group (15 weeks versus 10 weeks). It was not possible to explore the association between ART and miscarriage in this population, due to the likely differential ascertainment of pregnancy losses in the NSHPC, according to a woman's contact with antenatal services, knowledge of her HIV status and timing of the miscarriage.

Changes in the demographic profile of the women were also apparent. In the early 1990s, almost half of all pregnancies reported to the NSHPC were in women who acquired HIV through injecting drug use (IDU) or whose partner was a drug user, declining to only 3% in recent years. Similar patterns were observed elsewhere in Europe and in the United States (US) (European Collaborative Study, 1996a; European Collaborative Study, 2001; Martinelli *et al.*, 2008; Peters *et al.*, 2008). In later years the majority of pregnancies were in women originating from areas with generalised HIV epidemics, particularly sub-Saharan Africa (accounting for over 75% of pregnancies). This is consistent with the much higher prevalence of HIV, within the UK, in women born in sub-Saharan Africa (2.5% in 2007) than in those born in the UK (0.05% in 2007) (Health Protection Agency, 2008). This pattern also reflects the overall increase, within the adult population, in the number of newly diagnosed infections acquired heterosexually in Africa, which rose from around 500 in 1995 to over 3000 in 2004 (63% of which were in women) (The UK Collaborative Group for HIV and STI Surveillance, 2005). There was also a small but significant

increase over time in the proportion of pregnancies in women born in Asia (0% in 1990-1993 to 2.2% in 2004-2006), and in those of Caribbean origin (1.4% to 3.7%). Although there was evidence of an increase in new diagnoses in Caribbean populations between 1997 and 2001 (Dougan *et al.*, 2004), no such trend has been observed among Asian populations in the UK (Ades *et al.*, 1999; Cliffe *et al.*, 1999; The UK Collaborative Group for HIV and STI Surveillance, 2006), despite increasing prevalence rates in some parts of Asia (UNAIDS/WHO, 2007). In recent years, several pregnancies in young women who acquired HIV vertically from their own mothers were notified to the NSHPC. Similar cases have been reported in other countries (Brogly *et al.*, 2007; Ezeanolue *et al.*, 2006; Thorne *et al.*, 2007; Zorrilla *et al.*, 2003), and are likely to increase in number in the future, as girls infected perinatally in the early years of the HIV epidemic reach childbearing age.

There were also changes in the geographic origin of pregnancy reports across the British Isles. Although reporting rates (number of reports per million women of childbearing age) remained highest in London throughout the study period, the proportion of pregnancies reported from elsewhere in England increased markedly, from 13% in 1997-1999 to 43% in 2004-2006. This trend was likely due to several factors; firstly it probably reflected differences in the prevalence of HIV among women giving birth, which rose from an estimated 0.19% to 0.42% in London, and 0.02% to 0.14% in the rest of England between 1997 and 2007 (Health Protection Agency, 2008; The UK Collaborative Group for HIV and STI Surveillance, 2007). Secondly, there were regional differences in antenatal detection rates over time, due to earlier introduction of routine antenatal screening in London than elsewhere, and initially higher uptake (Townsend, Cliffe, & Tookey, 2006). Finally, the UK government policy of dispersing asylum seekers from the South East of England to

other parts of the country is also likely to have contributed to the increase in reports from areas outside of London (Immigration and Asylum Act, 1999; National AIDS Trust, 2006; The UK Collaborative Group for HIV and STI Surveillance, 2007).

7.2 Trends in uptake of interventions – antiretroviral therapy and mode of delivery

The combination of ART, elective caesarean section and avoidance of breastfeeding has been highly successful in reducing the risk of mother-to-child HIV transmission (Thorne & Newell, 2003), as was shown in Chapter 3 of this thesis. Following the licensing of zidovudine for use in pregnancy in 1994, uptake increased rapidly, reaching over 50% in 1997. Zidovudine monotherapy was gradually replaced with more effective dual therapy regimens and then with highly active antiretroviral therapy (HAART) from around 1998 onwards. Currently, almost all diagnosed HIV-infected women (98%) take ART when pregnant. Although most receive HAART, a small proportion take zidovudine monotherapy, generally in accordance with the BHIVA Guidelines. Among women on HAART, the use of regimens containing protease inhibitors (PI) increased dramatically, from about a third in 1999 to over two thirds in 2006. Women diagnosed antenatally and those with higher CD4 counts were more likely to be on PIs than those diagnosed before pregnancy, or those with lower CD4 counts, respectively. This suggests that the increase in PI-based HAART was probably associated with concerns about nevirapine hepatotoxicity in women with CD4 counts >250 cells/µl (Lyons *et al.*, 2003; Mazhude *et al.*, 2002).

The increasing use of ART over time is likely to have contributed to the observed patterns in clinical and immunological factors, with a rise in median CD4 counts and decline in plasma RNA viral loads, and in the proportion of women reported to have

HIV-related symptoms (Chapter 3). Improvements in maternal immunological factors may also reflect earlier diagnosis of HIV infection associated with the introduction of the universal antenatal screening policy. In the UK in recent years (2000-2004), women who were newly diagnosed antenatally were less likely to have been diagnosed late (i.e. with a CD4 count below 200 cells/µl) than those diagnosed in other settings (20% versus 38%) (Chadborn *et al.*, 2006). Among pregnant women reported to the NSHPC, HIV-related symptoms declined sharply from over 20% in the 1990s to 11% between 2000 and 2006, suggesting a possible link with the introduction of the screening policy. However, trends in CD4 count and viral load were more gradual. Although the decrease in viral load over time was undoubtedly associated with a rise in uptake of effective ART, the trend in undetectable viral load (<50 copies/ml) may have been slightly overestimated, since more sensitive assays tended to be available in later years (Mulder *et al.*, 1994; Mulder *et al.*, 1997).

Following evidence linking elective caesarean section with a reduction in the risk of MTCT in the mid-1990s (European Collaborative Study, 1994; European Mode of Delivery Collaboration, 1999), the proportion of women delivering by planned pre-labour caesarean section increased from around 40% before 1998 to 66% in 1999. The success of HAART, however, has led to uncertainty about the additional benefit of elective caesarean section for women achieving undetectable HIV RNA plasma viral load by the time of delivery. Guidelines now suggest that such women may opt for a vaginal delivery (BHIVA/CHIVA, 2008); planned vaginal deliveries rose from 17% to 28% between 1999 and 2006, with a corresponding decline in elective caesarean sections from 66% to 50%. This recommendation may also have contributed to the observed increase in emergency caesarean sections, which could result from unexpected complications arising during planned vaginal deliveries; the

increase in proportion of emergency procedures being carried out at term (49% in 1999 to 61% in 2006) supports this interpretation (Chapter 3). Uncertainty around the risk of transmission in cases where duration of ruptured membranes is prolonged may also lead to additional emergency caesarean sections. The impact of policies and recommendations around management of delivery needs to be monitored closely, as unintended effects may occur. For instance, while elective caesarean section deliveries are likely to be scheduled at times when HIV specialist midwives and obstetricians are available, vaginal deliveries and emergency caesarean sections may occur unexpectedly, when specialist staff are less likely to be on duty.

7.3 Mother-to-child transmission

Overall mother-to-child transmission rates among diagnosed HIV-infected women in the UK and Ireland declined from 24% in 1993 to 2% in 1998 (Chapter 3); these rates were slightly different from previously published estimates for 1990-1998 (Duong *et al.*, 1999), due to the inclusion of late reports and fluctuation caused by the relatively small number of births during this period. The analysis described in Chapter 3 indicated sustained low transmission rates from 1998 onwards. Between 2000 and 2006, the overall transmission rate was 1.2%, with a non-significant decline from 1.6% in 2000-2002 to 1.0% in 2003-2006. These low rates are consistent with reports from elsewhere in Europe and the United States (US) (Centers for Disease Control and Prevention, 2006; European Collaborative Study, 2005d; Peters *et al.*, 2008; Warszawski *et al.*, 2008). Similar transmission rates were observed among women on HAART who had either elective caesarean section or planned vaginal deliveries (0.7% in both groups). The transmission rate was particularly low (0.1%) in the 2117 women on HAART who achieved viral

suppression near delivery, with only three transmissions reported, two of which probably occurred *in utero*, based on the timing of their first positive test result.

In cases where transmission occurred despite HAART and planned vaginal or elective caesarean section delivery, most infections could be explained by failure to reduce viral load, mainly due to short duration of treatment or adherence problems, or to *in utero* transmission. Of the nine infected children born to women with low or undetectable viral loads, four had detectable virus at birth and were probably infected *in utero*. In the absence of prophylactic interventions, most transmission takes place around the time of delivery or postnatally (through breastfeeding) (Newell, 1998). However, available interventions have had a greater impact on reducing intrapartum and postpartum transmission, and cases of *in utero* transmission have been highlighted in recent years (AIAU, NSHPC, & CHIVA, 2007; Warszawski *et al.*, 2008). In non-breastfeeding populations in the pre-HAART era, intrauterine transmission accounted for around a quarter of transmissions (Thorne & Newell, 2003), whereas in a French study of ART-treated women delivering between 1997 and 2004, over 40% of infants born to women with viral loads <400 copies/ml were presumed to have been infected *in utero* (Warszawski *et al.*, 2008). Information on HIV RNA PCR tests at birth were not explicitly collected for infants in this study, so it was not possible to explore timing of infection overall.

There were no transmissions reported in over 450 infants born to women who received zidovudine monotherapy in the HAART era (2000-2006) and delivered by elective caesarean section. This finding suggests that selective monotherapy is also a reasonable strategy for preventing MTCT, particularly as low rates of drug resistance have been reported among women opting for this approach (Larbalestier *et al.*, 2003; Read, Costelloe, & Mullen, 2006). There may also be additional benefits of

monotherapy, including a reduced risk of toxicity to the mother and infant (BHIVA/CHIVA, 2008), as well as potential benefit in relation to future treatment options. It should be noted, however, that these findings are based on a population in which zidovudine monotherapy was generally used selectively, in accordance with the BHIVA Guidelines (BHIVA/CHIVA, 2008). Furthermore, the fact that the majority of women on monotherapy had detectable viral loads near the time of delivery underlines the need for careful management of delivery, probably by caesarean section. This approach, as an alternative to HAART, is therefore only appropriate in settings with access to safe surgical delivery and appropriate post-operative care.

In multivariable analysis, both lack of ART and vaginal delivery, particularly if unplanned, were independently associated with transmission, and remained so after further controlling for plasma viral load near delivery. The lack of a statistically significant association between maternal CD4 cell count and MTCT was likely due to small numbers, since low CD4 has been shown to be associated with an increased risk of transmission (European Collaborative Study, 2001), and MTCT rates tended to be higher in women with low CD4 (1.5% in women with CD4 <200 cells/µl, compared with 0.8% in those with CD4 ≥500 cells/µl).

Before the widespread use of HAART, prematurity was identified as a risk factor for transmission (European Collaborative Study, 1999). However, in this analysis, the increased risk of transmission associated with very premature delivery in the main multivariable analysis was not observed in a similar analysis restricted to women on HAART, although it is possible that this was due to lack of statistical power, as only four very premature infants were infected. Girls were at increased risk of infection compared with boys, although the association was no longer significant when the

analysis was restricted to cases where maternal viral load was recorded, possibly due to the reduced number of cases in the analysis. A sex difference in mother-to-child transmission rates has been reported in other studies, both for HIV and for hepatitis C virus (Biggar *et al.*, 2006; European Paediatric Hepatitis C Virus Network., 2005; Piwoz *et al.*, 2006; The Breastfeeding and HIV International Transmission Study (BHITS) Group, 2004; Thorne & Newell, 2004a). In some studies, the association between sex and transmission was restricted to infants infected *in utero*, suggesting a higher risk of intrauterine infection in girls, or of fetal death following intrauterine infection in boys (Piwoz *et al.*, 2006; Thorne & Newell, 2004a). There was no evidence of the latter in this study, with twice as many stillborn girls reported as boys. Although the reasons underlying this finding remain unclear, there is now a consistent body of evidence supporting an association between risk of MTCT and sex.

Viral load was associated with 2.4-fold increase in transmission for each $\log_{10}$ increase in viral load copies, which was consistent with the literature (Cooper *et al.*, 2002; European Collaborative Study, 2005d; Warszawski *et al.*, 2008). In multivariable analysis, adjusting for viral load led to an increase in the adjusted odds ratio (AOR) for the association between vaginal delivery and MTCT; this can be explained by the observation that most vaginal deliveries in recent years were planned, and therefore tended to be in women with low or undetectable plasma viral load. In other words, the association between vaginal delivery and transmission was negatively confounded by viral load. Adjusting for viral load also reduced the AOR for the association between lack of ART and transmission from 9.1 to 3.2; this is because viral load is on the causal pathway, with ART affecting the risk of transmission by reducing viral load. Because viral load was less likely to be reported

for untreated women, restricting the analysis to women with viral loads reported led to some selection bias.

Among women on HAART, there was no significant difference in transmission rates by type of regimen (0.9% for regimens containing non-nucleoside reverse transcriptase inhibitors [NNRTIs] and 1.1% for PI-containing regimens), even though NNRTI-based HAART, when initiated in pregnancy, has been shown to be associated with a more rapid decline in plasma viral load than PI-based regimens (European Collaborative Study, 2007). However, although there were around 1800 women in each of the two groups, the ability to detect a difference was limited by the low overall transmission rates. There was evidence that women on PI-based HAART were diagnosed more recently than those on NNRTI-based HAART and were less immunocompromised; this pattern was probably due to avoidance of nevirapine-based regimens in women with CD4 counts above 250 cells/µl in recent years, owing to toxicity concerns (BHIVA, 2005b; Lyons *et al.*, 2003). Although a difference in the risk of transmission by type of regimen cannot be ruled out, it is reassuring that rates were around 1% in both groups.

There was evidence that being on HAART at conception was associated with a lower risk of transmission than starting HAART in pregnancy. Longer duration of HAART was also associated with a reduced risk of transmission, even after adjusting for viral load. Both of these observations could be due in part to a lower risk of intrauterine transmission when HAART is started earlier. In these analyses, plasma viral loads closest to delivery were used, which might explain why timing of initiation of HAART remained associated with transmission after adjusting for viral load, since viral loads later in pregnancy would not necessarily reflect the infant's exposure to high maternal viral loads at earlier stages of pregnancy.

Children whose infection status had not yet been reported were more likely than those with known infection status to have recognised risk factors for transmission. Among those with unreported infection status, the excess of children born to black African mothers occurred because infection status was more likely to be missing for recent cases (due to reporting delay), when the proportion of African women was higher (80% in 2006, versus 71% in 2000). However, although this bias could potentially lead to an underestimate of the overall transmission rate, any effect is likely to be small. Imputing infection status on the basis of other available risk factors did not alter the overall transmission rate.

These findings, showing low rates of MTCT in appropriately managed pregnancies, are reassuring. However, because of the small number of transmissions occurring in recent years, statistical power was limited in these analyses, particularly when comparing subgroups of women with very low transmission rates.

7.4 Adverse effects of antiretroviral therapy

The association between ART and a number of adverse pregnancy outcomes was explored in this thesis: stillbirth, neonatal death, and pregnancy complications such as pre-eclampsia were explored in Chapter 4, and prematurity and birth weight were covered in Chapter 5.

Stillbirth, neonatal mortality and other pregnancy complications

The neonatal mortality rate among infants born to HIV-infected women in the UK and Ireland was 3.6 (95% CI: 2.4-5.1) per 1000 live births (Chapter 4); this was lower than rates of 6-7 per 1000 live births reported for HIV-infected women

enrolled in the ECS (1985-2003) (European Collaborative Study, 2004a), but was in line with population rates for England, Wales and Northern Ireland, which declined from 3.9 (95% CI: 3.7-4.0) to 3.4 (95% CI: 3.3-3.6) per 1000 between 2000 and 2006 (Confidential Enquiry into Maternal and Child Health, 2008). In the NSHPC, the stillbirth rate of 10.9 (95% CI: 8.8-13.4) per 1000 births was substantially and significantly higher than the population rate of 5.3 (95% CI: 5.1-5.5) per 1000 births in 2006 (Confidential Enquiry into Maternal and Child Health, 2008). In an analysis by Suy and colleagues, in which fetal death was defined as intrauterine death after 22 weeks (a slightly lower cut-off than the one used here), rates were significantly higher in HIV-infected (61 per 1000 deliveries) than uninfected women (5 per 1000 deliveries), although the analysis included only 82 HIV-infected women (all delivering between 2001 and 2003) (Suy *et al.*, 2006). Although the reasons for these differences are unclear, possible explanatory factors include differences in the risk profile of HIV-infected women compared with the wider population, factors related to HIV infection or disease, and adverse effects associated with ART.

There was some evidence in support of an association between ART and stillbirth: the rate in women on HAART in pregnancy (11 per 1000 births) was significantly higher than the rate in those on monotherapy (3 per 1000 births), which was more in line with the population rate. However, the association was reduced and only borderline significant after adjusting for CD4 count and multiple pregnancy, partly due to a reduction in the odds ratio from 4.0 (OR) to 3.1 (AOR), and partly due to small numbers (only three stillbirths in women on monotherapy). Furthermore, because women who take monotherapy in pregnancy tend to start treatment slightly later than those who start HAART (Chapter 5), and stillbirths tend to occur earlier than live births (Chapter 4), some bias may occur, with women intending to start

monotherapy being less likely to initiate treatment prior to a stillbirth than those planning to start HAART. Although this finding is consistent with the evidence on HAART and prematurity, it should therefore be interpreted with caution. Information on stillbirths has been reported in a number of studies, but most have not had the power to detect an association with ART, with only a few stillbirths reported (Cotter *et al.*, 2006; Ekouevi *et al.*, 2008; Tuomala *et al.*, 2002; Tuomala *et al.*, 2005; Watts *et al.*, 2004a). In a cohort of HIV-infected women delivering between 1985 and 2003 (n=472) reported in the publication by Suy and colleagues, mentioned above, the incidence of fetal death was 17.0 per 1000 deliveries (95% CI: 7.3-33.4), and was significantly higher in women on HAART prior to pregnancy (OR=7.9, p=0.005), although the authors were not able to adjust for other variables.

Information on pregnancy complications other than stillbirth was collected through the obstetric scheme of the NSHPC from mid-2004 onwards. Complications were reported in 7.7% of pregnancies, and included a wide range of obstetric problems and conditions, including pre-eclampsia and gestational diabetes (Chapter 4). Overall, complications were associated with older maternal age and multiple pregnancy, consistent with patterns in the general population (Luke & Brown, 2007; Rao, Sairam, & Shehata, 2004). Complications were also more likely in women with HIV-related symptoms or low CD4 count, which is consistent with the generally higher rates of postpartum complications in these women (Duarte *et al.*, 2006). The prevalence of complications was slightly higher in women on non-PI-based HAART than in those on monotherapy, but the association was mostly explained by clinical status and CD4 count and disappeared in adjusted analyses. Pregnancy complications were significantly more likely in women on HAART at conception than in those starting in pregnancy (11% versus 7%), even after adjusting for other factors. Upon

further investigation, the association was found to be driven by one particular adverse outcome, pre-eclampsia, which has been linked with early HAART (Suy *et al.*, 2006) and was explored separately. Even though the definition of pregnancy complications used in this analysis was broad (no reported complications were excluded), associations with known risk factors for pregnancy complications were detected in this population of HIV-infected women. However, rates of specific complications, such as pre-eclampsia and gestational diabetes, were somewhat lower than expected, compared with population rates (National Institute for Clinical Excellence, 2008; Sibai, Dekker, & Kupferminc, 2005), possibly due to under-reporting.

In light of concerns raised in a Spanish study (Suy *et al.*, 2006) about a possible association between HAART at conception and pre-eclampsia, this outcome was explored in more detail in the NSHPC (Chapter 4). While the interactions between HIV, ART and pre-eclampsia are not fully understood, there is some evidence to suggest that HIV reduces the risk of pre-eclampsia in untreated women (Hall, 2007; Stratton *et al.*, 1999). Because information on pre-eclampsia was only collected from 2004 onwards in the NSHPC, few untreated women were reported (n=53), with one case of pre-eclampsia. It was therefore not possible to comment on differences between treated and untreated women, or between HIV-infected and uninfected women, due to the lack uninfected controls. The overall rate of reported pre-eclampsia was 2.1%, which is consistent with rates of 2-5% observed in large population-based studies in Europe and North America (Catov *et al.*, 2007; Dahlstrom *et al.*, 2006; Wallis *et al.*, 2008; Xiong, Fraser, & Demianczuk, 2002). The causes of pre-eclampsia are unknown, although a number of risk factors have been identified, including extremes of maternal age, nulliparity, multiple pregnancy, chronic hypertension, and maternal infections (Conde-Agudelo & Belizan, 2000;

Conde-Agudelo, Villar, & Lindheimer, 2008; Sibai, Dekker, & Kupferminc, 2005). The main clinical manifestations of pre-eclampsia are hypertension and proteinuria (abnormal protein levels in the urine), but can also include pulmonary oedema, thrombocytopenia or neurological symptoms, as well as reduced amniotic fluid and fetal growth restriction, and in severe cases can lead to eclampsia or haemolysis, elevated liver enzymes or low platelet counts (HELLP) syndrome (Sibai, Dekker, & Kupferminc, 2005). Pre-eclampsia is an important cause of maternal morbidity, particularly in developing countries, and eclampsia accounts for 12% of maternal deaths worldwide (World Health Organization, 2005).

Pre-eclampsia was reported in 11% of all pregnancies delivered prematurely (Chapter 4); rates of preterm delivery in affected women were high, at 70%, compared with a reported range of 15-67% (Sibai, Dekker, & Kupferminc, 2005). The association between pre-eclampsia and parity was consistent with other studies (Conde-Agudelo & Belizan, 2000; Dekker & Sibai, 2001): in multivariable analysis, parous women were about half as likely as nulliparous women to develop pre-eclampsia. HIV-related symptoms and low CD4 count were associated with significantly increased rates of pre-eclampsia; this was not consistent with the suggestion that immune suppression could explain the low rates of pre-eclampsia reported in one cohort of untreated HIV-infected women (Wimalasundera *et al.*, 2002). There is ongoing debate about the relationship between untreated HIV and pre-eclampsia (Hall, 2007), with at least one study having found no reduction in pre-eclampsia rates in untreated HIV-infected women (Frank, Buchmann, & Schackis, 2004).

Among women on HAART, non-PI-containing regimens and initiation of HAART before pregnancy were associated with an increased risk of pre-eclampsia

(AOR=1.75 and 1.62, respectively), which in both cases was statistically significant only in women with CD4 counts ≥200 cells/µl (AOR=1.94 and 1.89, respectively). These findings are consistent with those reported by Suy and colleagues, and support the premise that earlier initiation of HAART is associated with an increased risk of pre-eclampsia (Suy *et al.*, 2006). However, it should be noted that overall pre-eclampsia rates among these HIV-infected women were on the low end of the range for HIV-uninfected populations, even among those who started HAART before pregnancy. Furthermore, given the likely under-ascertainment of pregnancy complications, and lack of specific case definitions, these findings should be interpreted with caution.

There is some evidence of a link between PIs and gestational diabetes (Watts *et al.*, 2004a). In the NSHPC, gestational diabetes was reported in only 0.8% of pregnancies (Chapter 4), which is notably lower than the average for England and Wales of 3.5% (National Institute for Clinical Excellence, 2008). There was no significant difference by type of HAART, although the rate tended to be lower with PI-based HAART than with non-PI-based HAART (0.7% versus 1.4%), which contradicts findings of increased rates of gestational diabetes associated with PI use in other studies (Gonzalez-Tome *et al.*, 2008; Watts *et al.*, 2004a).

Despite the high response rates to the question on pregnancy complications (93%), there is likely to have been some under-reporting. In particular, ascertainment of specific problems was probably incomplete due to the open nature of the question and lack of precise case definitions for individual problems. Pre-eclampsia was mentioned as an example in the question and reporting may therefore be more complete for this problem than for others. However, the spectrum of pre-eclampsia-related conditions means that misclassification is also likely to have occurred.

Diagnosis of some complications including pre-eclampsia relies on a series of measurements taken at specific intervals, but details of how diagnosis was established were not collected in this study. Nevertheless, known risk factors were significantly associated with both overall pregnancy complications and pre-eclampsia, and the observed pre-eclampsia rate was comparable to population rates (albeit on the low end of the range).

Congenital abnormalities

The overall congenital abnormality rate among live and stillborn infants in this population was 2.8% (2.1% excluding minor defects) (Chapter 4), which is consistent with national population estimates of 2-3% for major abnormalities in England and 2.2% for Europe as a whole (calculated from EUROCAT data tables, 1980-2006) (EUROCAT, 2004; EUROCAT, 2008).

Abnormality rates did not differ significantly by timing of ART in pregnancy, or by type of first trimester ART (PIs and/or NNRTIs). These findings support those of other European and American studies (Bucceri *et al.*, 2002; European Collaborative Study, 2005a; Mandelbrot *et al.*, 2001; Watts *et al.*, 2007) and of the Antiretroviral Pregnancy Registry (APR) (Covington *et al.*, 2004; Watts *et al.*, 2004b). Because of concerns raised about two specific antiretroviral drugs, efavirenz and didanosine (Antiretroviral Pregnancy Registry Steering Committee, 2008; De Santis *et al.*, 2002; Fundaro *et al.*, 2002), abnormality rates in these groups were investigated separately. No significant increase in abnormalities was detected following early exposure to efavirenz (2.4% of 205 infants) or didanosine (3.4 % of 174 infants). In 2007, the Women and Infants Transmission Study (WITS) in the US reported an increase in the rate of hypospadias (AOR=10.7, 95% CI: 2.1-54.1, p=0.004) associated with

early zidovudine exposure (Watts *et al.*, 2007). There were 12 reported cases of hypospadias among infants notified to the NSHPC, and rates were similar following early or late ART exposure and according to whether or not early treatment included zidovudine.

Congenital abnormality rates were higher in boys than in girls, and in infants born to white, symptomatic women. The excess of abnormalities in boys was mainly accounted for by genital abnormalities (mostly undescended testes and hypospadias), all of which were in boys. When excluding genital abnormalities, the difference was no longer significant (2.8% in boys versus 2.2% in girls, p=0.098). There was also an excess of polydactyly in boys, which has been observed in a few studies, for example in Chile and Hungary (Bellovits, 2003; Cifuentes *et al.*, 1996). The increased rate in symptomatic women was also observed in an earlier analysis of NSHPC data, which included 3100 infants (Townsend *et al.*, 2006), as was the finding of an increased risk for infants born to white women compared with those born to black African women. The association with ethnic group was likely due to variation in other maternal characteristics or exposures, which are not routinely collected through the surveillance system. The rate among infants exposed only to NRTIs in the first trimester was also higher, although not significantly, than in infants exposed to other drug classes; this could be a chance finding (based on only eight abnormalities in 148 infants) or could reflect the different risk profile of their mothers, who were more likely to be women who were young, white and/or had acquired HIV through IDU and were reported in the mid-1990s. The excess of infants with renal dilatation among those with early ART exposure could also be a chance finding, but rates of this abnormality within the NSHPC and in other studies should continue to be monitored.

Reports of congenital abnormalities in this population are likely to be relatively complete, at least for those detected in the first few weeks of life, due to the complementary obstetric and paediatric reporting systems. Nevertheless, a small number of abnormalities not apparent at birth might have remained unreported, either because the birth was only notified through the obstetric scheme, or because the abnormality was detected only after the last paediatric report to the NSHPC. It was also not possible to routinely check the details of reported abnormalities, for example if a defect was specified by one respondent but not the other. However, discrepancies in terms of the nature of reported abnormalities were rare. Although there is incomplete ascertainment of pregnancy terminations through the NSHPC, those carried out after a congenital anomaly scan are likely to be well reported, since contact with antenatal services will already have occurred.

Infants missing information on presence of congenital abnormalities were more likely to be premature, a factor which was associated with having an abnormality; however, these infants were no more likely to have had early ART exposure that those with information provided, and it is therefore unlikely that this will have substantially affected the findings regarding the association with ART. Although information on maternal ethnicity, age, injecting drug use and clinical status was available, data on other potential confounders such as maternal smoking and diet during pregnancy, concurrent infections and non-HIV medication were not.

This analysis included over 8200 infants (1700 with early ART exposure), with sufficient power (~80%) to detect a 1.5-fold increase in abnormalities associated with first trimester exposure. However, at least 370 exposures to any specific drug are required to detect a two-fold increase in overall risk of congenital abnormalities (from 3% to 6%) with 80% power, and even larger numbers would be required to

detect an association with a particular type of abnormality. Nevertheless, these results provide some reassurance that exposure to ART *in utero* does not pose a major risk of fetal anomaly, particularly given the consistent findings across many large-scale observational studies including the European Collaborative Study, the WITS study and the APR (Antiretroviral Pregnancy Registry Steering Committee, 2008; European Collaborative Study, 2005a; Watts *et al.*, 2007). Continued monitoring of congenital abnormalities in infants born to women on ART in early pregnancy is essential, particularly as new drugs and new combinations of drugs are introduced. Difficulties around statistical power in analyses involving individual drugs or types of abnormalities could potentially be overcome in the future by pooling data from several of these studies.

Prematurity

In developed countries, prematurity is the leading cause of perinatal mortality, accounting for up to 75% of perinatal deaths (Ananth & Vintzileos, 2006). Although the majority of premature infants do survive, they are at increased risk of serious morbidity, including respiratory distress and gastrointestinal complications, as well as neurodevelopmental impairment. Preterm birth can occur following spontaneous preterm labour (40-45% of preterm births in non-HIV populations), preterm premature rupture of membranes (25-30% of cases) or for medical indication with induction of labour or delivery by caesarean section (30-35% of cases) (Goldenberg *et al.*, 2008). Risk factors for preterm birth include socio-demographic characteristics, nutritional status, obstetric history and infection (Table 7.1), many of which are associated with activation of inflammatory pathways (Goldenberg *et al.*, 2008). Differences in prematurity by ethnicity have been reported in Europe,

including in the UK, with black African women having higher prematurity rates than white women (Aveyard *et al.*, 2002; Gardosi & Francis, 2000; Patel *et al.*, 2004; Slattery & Morrison, 2002). There are clear ethnic differences in prematurity rates in the US, but it is unclear whether socio-demographic factors, including inequalities in access to health insurance and healthcare, are responsible. In many immigrant groups in the US, prematurity risk increases with longer duration spent living in the US, suggesting a role for cultural or social factors (Goldenberg *et al.*, 2008). Use of illicit drugs in pregnancy is also associated with an increased risk of prematurity, as are extremes of maternal age.

In this thesis, the association between ART and prematurity was first explored in the NSHPC, and subsequently in a combined analysis with two other studies.

Table 7.1 Risk factors for preterm birth

Socio-demographic factors
Black, African-American or Afro-Caribbean ethnicity
Low socio-economic/educational status
Low and high maternal age (<20 or >35 years of age)
Single marital status
Long working hours / hard physical labour
Obstetric factors
Short interpregnancy interval
Prior preterm birth
Multiple pregnancy
Obstetric complications (poly/oligohydramnios, placental abruption/praevia)
Congenital abnormality
Maternal health factors
Low body-mass index / poor nutritional status
Maternal medical problems (thyroid disease, asthma, diabetes, hypertension)
Depression
Smoking, drug or alcohol abuse
Intrauterine infection
Genital tract infection / bacterial vaginosis

Derived from: (Goldenberg *et al.*, 2008; Slattery & Morrison, 2002)

NSHPC analysis

Overall prematurity rates and risk factors

The overall prematurity rate in this population was 13.3%, more than twice the rate in the general population. In 2005, 6.2% of live singleton births in England occurred before 37 weeks, according to recent data from the Office for National Statistics, with substantial variation between ethnic groups; rates were 6.1% in infants classified as 'white British', 7.0% in black African infants and 9.7% in black Caribbean infants (Moser, Stanfield, & Leon, 2008). Although there were no national data on trends in gestational age in the UK until 2005 (Moser, Stanfield, & Leon, 2008), the rate of low birth weight (<2500 g) in singleton infants in England and Wales remained relatively constant between 1983 (5.8%) and 2000 (6.1%) (Maher & Macfarlane, 2004). In this population of HIV-infected women, IDU and maternal HIV-related symptoms were significantly and positively associated with prematurity, but ethnic group and maternal age were not. The fact that black women were not at increased risk of premature delivery could be due to a high baseline prematurity rate in white HIV-infected women; higher rates of IDU were reported in this group, and it is likely that rates of other high risk behaviours (smoking, alcohol abuse) were also increased in these women. IDU was significantly associated with prematurity in this population, even though information was on IDU as the route of HIV acquisition, rather than drug use during pregnancy. Consistent with population trends in birth weight (Maher & Macfarlane, 2004), there was no detectable change in the overall prematurity rate over time. Low CD4 count and maternal HIV-related symptoms were also associated with prematurity. The association between maternal clinical factors and prematurity in HIV-infected women has been reported elsewhere (European Collaborative Study, 2004a; European Collaborative Study and the Swiss

Mother + Child HIV Cohort Study, 2000; Schulte *et al.*, 2007), and in the general population, markers of poor maternal health, including low body mass index and chronic medical conditions, tend to be associated with an increased risk of preterm delivery (Haas *et al.*, 2005).

ART and prematurity

The prematurity rate among women on HAART was 1.6 times higher than in those on monotherapy or dual therapy, and there was some evidence that the association was stronger at earlier gestational ages, with adjusted odds ratios of 2.7-2.8 for delivery at <35 weeks or <32 weeks. There was no difference in prematurity rates between PI-containing (14.3%) and NNRTI-containing (13.5%) HAART, despite substantial numbers of exposures to both types of HAART; these findings differ from some other studies, in which an increased risk of prematurity was detected only with PI-containing HAART (Cotter *et al.*, 2006; Schulte *et al.*, 2007). The association between HAART and prematurity remained after adjusting for known risk factors for prematurity, including maternal ethnic group, age, IDU and clinical status, as well as in separate analyses controlling for HIV RNA viral load and/or CD4 cell count.

The lack of change in prematurity rates over time, despite increasing use of HAART, was probably due to a concurrent decrease in other risk factors for prematurity including HIV-related symptoms and IDU (shown in Chapter 3). Although acquisition of HIV through IDU was associated with an increased risk of prematurity, IDU did not substantially confound the association between treatment and prematurity: excluding IDU from the multivariable analysis yielded an AOR of 1.46 (versus 1.51, a difference of 3%). The proportion of women who acquired HIV through IDU may not have reflected the true prevalence of IDU in pregnancy,

although in a recent London-based study of HIV-infected individuals, only 7.2% had a history of current or previous IDU (Mohsen, Murad, & Easterbrook, 2005). Failing to fully adjust for the effect of drug-use in pregnancy would tend to attenuate the relationship between treatment and prematurity, since IDU was associated with both prematurity and monotherapy.

There was some evidence that earlier initiation of HAART was associated with an increased risk of prematurity. When pregnancies in which treatment was initiated after 26 weeks were excluded, to avoid bias introduced by differences in opportunity for starting treatment according to timing of delivery, later initiation of HAART was associated with a significantly reduced risk of prematurity. This finding suggests a dose-response effect of HAART on duration of pregnancy. Few studies have explored the effect of duration of HAART exposure (Cotter *et al.*, 2006; European Collaborative Study, 2004a), probably because dates of treatment initiation are not always available, and because analysis is complicated by the fact that premature delivery naturally shortens the duration of antenatal treatment.

Compared with prematurity rates in ART-treated women, those in untreated women in the NSHPC were higher overall (17% versus 13%) and increased over time (from 11% in the early 1990s to 20% in 2000-2005). With the benefits of antenatal ART now widely accepted, the small proportion of women who are ART-naïve at delivery are usually untreated either because they decline treatment or because they deliver before treatment can be initiated (due to late booking for antenatal care and/or to premature labour or rupture of membranes). The prematurity rate among pregnancies in this group is therefore inherently higher than in treated women, and comparison of these two groups was therefore not appropriate. In addition, almost 40% of untreated women were reported before ART was widely used, at a time when many women

had acquired infection through drug use, and had a different risk profile to women reported later on (as shown in Chapter 3). For these reasons, pregnancies in untreated women were not considered an appropriate control group.

Mechanisms

Following initial concerns about HAART and prematurity, it was postulated that the balance of Th1 and Th2 inflammatory cytokines could play a role (see Box 1). This was investigated in a small study of 26 HIV-infected pregnant women, who were all on HAART throughout pregnancy (Fiore *et al.*, 2006). Interleukin (IL)-10, an anti-inflammatory cytokine, was shown to decline throughout pregnancy, while IL-2, a pro-inflammatory cytokine, increased (although not significantly), a pattern that is consistent with a reversal of the Th1 to Th2 shift. Furthermore, a more rapid increase in IL-2 was associated with an increased risk of prematurity.

Box 1: Summary of Th1 → Th2 pathway

There are two major subsets of CD4+ T helper cells, Th1 and Th2, which play complementary roles within the immune system by producing different types of cytokines. The two subsets mediate each other, Th1 producing a pro-inflammatory immune response, and Th2 an anti-inflammatory response (Male *et al.*, 2006). During pregnancy, an increase in Th2-type cytokines and suppression of Th1-type cytokines is required to avoid rejection of the fetus through an immune response to feto-paternal antigens. HIV infection is also characterised by a Th1 to Th2 shift. However, treatment with antiretroviral drugs seeks to reverse this process, and could therefore be detrimental to the maintenance of pregnancy (Fiore *et al.*, 2006; Male *et al.*, 2006).

This mechanism suggests that ART-associated preterm delivery would result from spontaneous induction of labour or membrane rupture, rather than other pathological processes. In the ECS, uninfected children born prematurely following exposure to

combination therapy tended to fare better in terms of growth indicators than did unexposed premature infants, suggesting an absence of underlying morbidity in these children (European Collaborative Study, 2004c). It was not possible, in the NSHPC, to definitively classify preterm deliveries as spontaneous or induced. Further research into the reasons for premature delivery in HIV-infected women on HAART is needed.

Findings in relation to existing literature

These results concur with those from other European studies showing an increased risk of prematurity associated with HAART (Boer *et al.*, 2007; European Collaborative Study, 2004a; European Collaborative Study and the Swiss Mother + Child HIV Cohort Study, 2000; Grosch-Woerner *et al.*, 2008; Martin & Taylor, 2007). Yet several large-scale US studies have failed to detect an association between HAART and prematurity (Tuomala *et al.*, 2002; Tuomala *et al.*, 2005; Watts *et al.*, 2004a). In addition, a number of smaller studies have shown no association between ART and prematurity, but in many cases there are clear methodological reasons why findings differed. For example, some early studies looked at combination therapy rather than HAART, and combined dual and triple therapy in the analyses. In a French intervention study in which no association between ART and prematurity was detected, dual therapy (n=445) was compared with a historical cohort of women on monotherapy (n=899) (Mandelbrot *et al.*, 2001). In a retrospective Italian study, a low rate of prematurity (10%) was reported in women on combination therapy, but the study included only 100 women and there were no controls (Bucceri *et al.*, 2002). More recently, a study from Brazil reported no association between ART and preterm delivery in multivariable analysis (Szyld *et al.*, 2006). However, the model was adjusted for mode of delivery, which although

associated with both treatment and prematurity, is not a confounder, since it does not in itself influence either factor. Mode of delivery is associated with type of treatment because of concurrent changes over time in use of ART and elective caesarean section (and in recent years because choice of ART influences delivery options). It is also affected by preterm delivery, since premature labour or rupture of membranes precludes delivery by elective caesarean section. In the Brazilian study, HAART was associated with a non-significant 1.6-fold increased risk of prematurity in univariable analysis, which is consistent with NSHPC findings (Szyld *et al.*, 2006). In one of the early US studies, combination therapy was not explicitly defined but probably included a substantial proportion of dual therapy regimens, since all deliveries occurred between 1990 and 1998 (Tuomala *et al.*, 2002).

In a published report from Africa, infants exposed to HAART as part of a prevention study carried out between 2003 and 2007 were compared with infants exposed to zidovudine and single-dose nevirapine in 2001 to 2003. Although there may have been other limitations in this historical comparison, issues around indication for treatment would have been avoided since only one treatment approach was used in each period. Gestational age was not available in the study, but low birth weight was found to be more prevalent in infants born to women on HAART than in those exposed to zidovudine (22% versus 12%) (Ekouevi *et al.*, 2008).

Despite the growing evidence supporting a link between HAART and prematurity, a meta-analysis published in 2007 concluded that there was no association between the two (Kourtis *et al.*, 2007). However, the analysis failed to address a number of methodological issues, including the possibility of bias in the comparison of treated and untreated women and combination of dual therapy and HAART, which could attenuate the association with exposure to more potent combinations of drugs.

Furthermore, in several of the studies included in the meta-analysis (Bellon Cano *et al.*, 2004; Cooper *et al.*, 2002; Lorenzi *et al.*, 1998; Mandelbrot *et al.*, 2001), only crude prematurity rates were available, and estimates were therefore not adjusted for any potential confounders. Finally, the conclusions put forward in the meta-analysis are in themselves contradictory, since it is suggested that although ART is not associated with preterm delivery, duration and type of ART may be.

Strengths and weaknesses of NSHPC analysis

Evidence to date linking ART and prematurity has arisen mainly from cohort studies; in contrast to other studies, which recruit selectively and require consent, the NSHPC provides comprehensive population-based data, thereby reducing the chance of selection or ascertainment bias. However, due to resource limitations and in order to maintain high response rates, the range of information collected on other prematurity risk factors was limited. Prior preterm delivery is an important risk factor on which information was not available through the study, and which has been postulated as a potential confounder in the association between ART and prematurity (Tuomala *et al.*, 2005; Tuomala & Yawetz, 2006); in one study of ART-exposed pregnant women, those on monotherapy were less likely than those on combination therapy to have had a prior preterm delivery (Tuomala *et al.*, 2005). Although it was not possible to adjust for history of preterm delivery in NSHPC analyses, stratifying by parity did not affect the findings, suggesting that any potential confounding by prior preterm delivery would be minimal. Information on other potential risk factors for prematurity, such as socio-economic status, smoking, and drug or alcohol abuse, was also not available through the surveillance system. However, despite substantial changes over time in the demographic characteristics of HIV-infected pregnant women, including risk factors for prematurity, the magnitude of the association with

HAART was similar in different time periods (1994-1999 and 2000-2005), suggesting that other factors were unlikely to have substantially confounded the association between ART and prematurity.

An important source of bias in observational studies exploring ART and premature delivery is indication for treatment (Tuomala & Yawetz, 2006). According to the BHIVA Pregnancy Guidelines, monotherapy should only be offered to women who have low viral loads (<6000-10,000 copies/ml) and do not require treatment for their own health (BHIVA, 2001; BHIVA/CHIVA, 2008); those on monotherapy may therefore be at lower risk of premature delivery than those who require more aggressive HIV treatment, due to differences in disease stage or other immunological factors. Specific details about indication for treatment were not available in this analysis, but information on HIV-related symptoms, CD4 cell count and viral load was. Adjusting for these factors, which contribute to the decision about type and timing of initiation of treatment, tended to increase the association between HAART and prematurity. There is also some recent evidence in the literature that the association may be independent of treatment indication: in an Italian study, combination therapy with PIs was associated with an increased risk of prematurity (32% versus 18% in those not exposed to PIs) after adjusting for treatment indication and other variables (Ravizza *et al.*, 2007). Information on reason for treatment is now being collected through the NSHPC.

Classification of antiretroviral therapy was according to the total number of drugs received in pregnancy. Although switches in regimens do occur, most are from one HAART regimen to another, rather than from monotherapy to HAART or vice versa. Treatment misclassification was therefore likely to be minimal. Only 70 pregnancies were excluded from the analysis due to insufficient treatment information, some of

which were undoubtedly in untreated women since a third occurred in the 1990s, and treatment was only available from 1994 onwards. The prematurity rate in these few pregnancies was similar to the overall rate, and excluding them is unlikely to have introduced significant bias.

Duration of pregnancy was explored as a categorical variable in these analyses, to avoid complications introduced by the censoring of pregnancies delivered by elective caesarean section at around 38 weeks gestation. Rates of caesarean section changed alongside uptake of ART, and it was therefore not possible to explore duration of pregnancy as a continuous variable without introducing bias. Nevertheless, the fact that the association between HAART and preterm delivery was observed for <37 weeks, <35 weeks and <32 weeks gestation suggests that pregnancy duration is affected across the spectrum of gestational ages, possibly slightly more so at earlier gestational ages. It was also not possible to explore the type of preterm deliveries associated with ART, as details regarding preterm labour or premature rupture of membranes were not systematically collected.

Birth weight

Compared with infants exposed to mono/dual therapy, HAART-exposed infants had lower birth weight after adjusting for gestational age (and controlling for maternal clinical status, IDU-acquired infection, ethnic origin and maternal age at delivery). In clinical terms the difference in mean birth weight and in *z*-scores was small, but may have implications for very premature infants who are also of low birth weight for gestational age. In the ECS, differences in birth weight *z*-score by type of maternal ART were detected; however, these varied by gestational age, with infants born at 34 to 36 weeks being heavier if exposed to combination therapy than if not exposed. There was no difference in *z*-scores for infants born before 34 weeks or at term

(European Collaborative Study, 2005). Few other studies have looked at birth weight standardised for gestational age, but very low birth weight (<1500 g) was associated with combination therapy in one US study (Tuomala *et al.*, 2002), and an increase in low birth weight over time has been reported in the ECS (European Collaborative Study, 2004a).

Conclusion

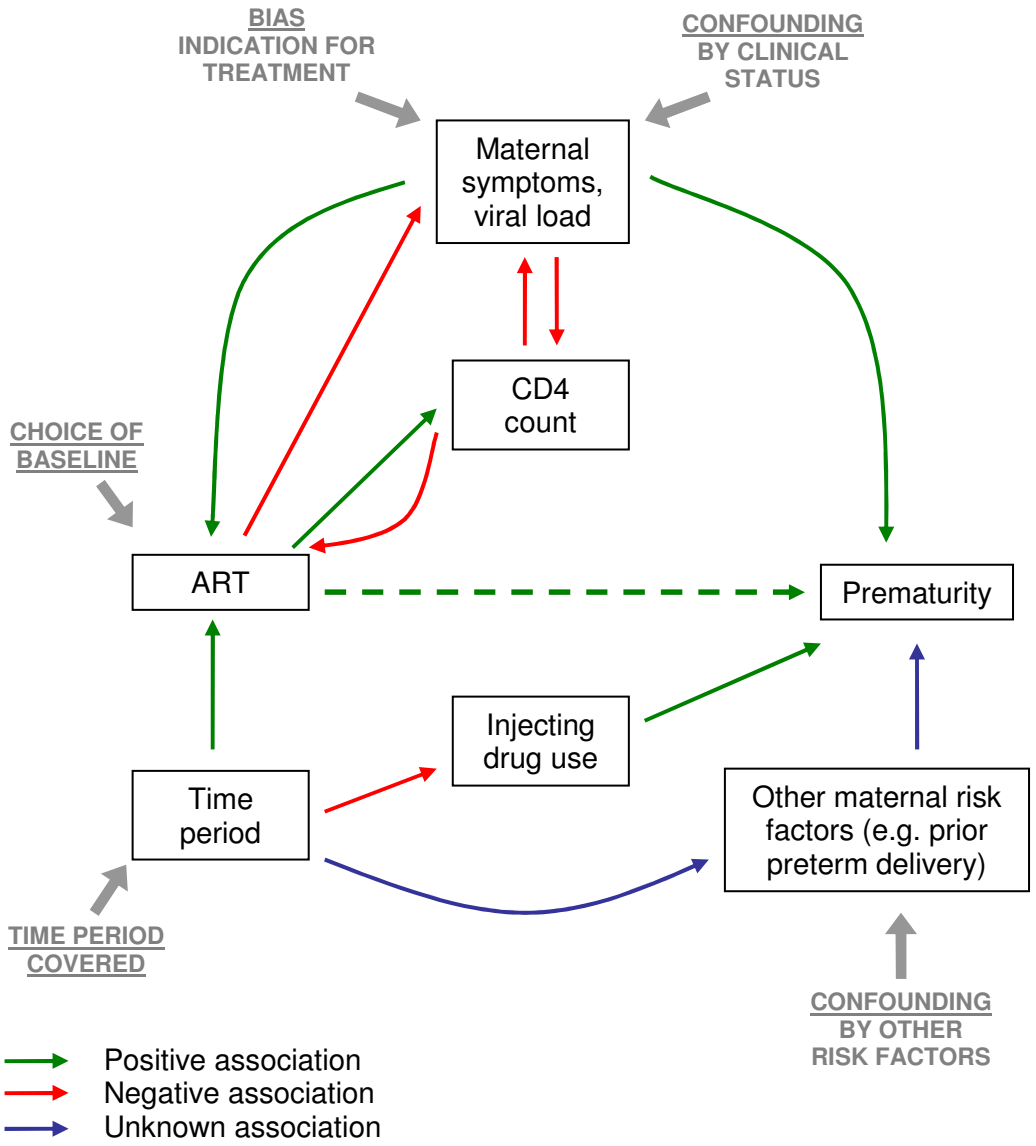
In conclusion, the association between ART and prematurity was consistent across unadjusted and adjusted analyses, and across a number of sub-analyses, and supports the findings from several other studies. The link between ART and premature delivery or low birth weight has now been reported in both cohort and non-consented surveillance or monitoring studies, and in different populations in Europe, the US and Africa, lending support to these findings. Nevertheless, it remains unclear why some studies have failed to detect an association between treatment and prematurity.

Comparative analysis

In order to investigate possible reasons underlying the conflicting findings with respect to ART and prematurity, NSHPC data were compared with data from the European Collaborative Study (ECS) and from the Pediatric Spectrum of HIV Disease (PSD) project in the US. Preliminary findings from the three studies included in the comparative analysis had suggested some differences between studies with respect to prematurity (European Collaborative Study, 2004a; Schulte *et al.*, 2007; Townsend *et al.*, 2007). This project set out to estimate the magnitude of the association between ART and prematurity using standard methods across the three studies, and to compare populations and methodologies in order to explain any differences between studies.

Figure 7.1 illustrates the associations between ART, prematurity and other potential risk factors, along with areas which could lead to differences in study findings.

Figure 7.1 Association between antiretroviral therapy, prematurity and other risk factors



In basic analyses comparing HAART with monotherapy, heterogeneity between studies in the association between ART and premature delivery was confirmed, implying that there were significant differences between studies in the association between ART and prematurity. Findings were consistent between the two European studies (ECS and NSHPC), with women on HAART in pregnancy at significantly increased risk of premature delivery compared with those on monotherapy; however in the US study (PSD), no such association was noted. Women on dual therapy in the PSD were at a lower risk of prematurity compared with those on monotherapy. These differences persisted in univariable and multivariable analyses, in basic and more refined multivariable models, at different gestational age cut-offs (<37 weeks and <32 weeks), and with PI and non-PI-based HAART. This heterogeneity precluded a combined analysis comparing HAART with monotherapy, although further investigation with dual therapy as the reference group, showing no significant heterogeneity, enabled a pooled analysis to be carried out subsequently.

There were consistent associations between other risk factors and prematurity across the three studies; for example, in the final multivariable models, which included all significant variables, maternal IDU was associated with a two-fold (or more) increased risk of prematurity in all three studies, as was the presence of HIV-related symptoms in the PSD and NSHPC. These observations suggest some level of comparability between studies, despite differences in the prevalence of these risk factors and in the way they were measured.

There were also some differences in the relationships between other risk factors and prematurity: ethnic group and year of delivery were significantly associated with prematurity only in the PSD. These findings reflect trends reported for the US population: crude prematurity rates in African American women in the US are higher

than in white women (17.8% versus 11.5%), a difference that is not fully explained by socio-economic or behavioural factors (Institute of Medicine, 2006). The overall prematurity rate is known to be increasing in the US, having risen from 10.6% in 1990 to 12.5% in 2004, although the causes of this rise are not fully understood (Institute of Medicine, 2006). The fact that unadjusted prematurity rates showed no change over time is likely due to the decline in other risk factors (IDU and HIV-related symptoms) among HIV-infected women, which would have counteracted the underlying baseline increase in prematurity associated with an increase in use of ART.

A number of methodological issues have been suggested as possible explanations for the discrepancies observed between different studies (Table 7.2) (European Collaborative Study, 2004a; Tuomala *et al.*, 2002; Tuomala *et al.*, 2005). Some of these points were addressed in the analysis presented in Chapter 5 and are discussed below.

Table 7.2 Putative explanations for conflicting findings regarding ART and prematurity

Issue	Possible explanation	Reference
Study design	Case ascertainment, inclusion criteria	(Townsend *et al.*, 2007)
Analytical approach	Differences in choice of reference group	(Townsend *et al.*, 2007)
Populations	Differences in baseline prematurity rate	(Patel, Thorne, & Newell, 2007)
	Population differences, e.g. in access to care and in proportion from minority groups	(Patel, Thorne, & Newell, 2007; Tuomala & Yawetz, 2006)
Bias and confounding	Lack of adjustment for other risk factors, including: - prior preterm delivery - duration of HAART - clinical disease stage or HIV viral load	(Tuomala & Yawetz, 2006)
	Differences in prescribing patterns, confounding by indication for treatment	(Tuomala & Yawetz, 2006)

Study design

Differences in methodology between studies could affect the observed association between treatment and pregnancy outcome; in a study by Tuomala and colleagues, which combined data from clinical trials and cohort studies, women in one trial were recruited at 20-30 weeks gestation (Tuomala *et al.*, 2002), thereby excluding those who failed to attend for antenatal care during that period, a factor potentially associated with prematurity risk as well as choice of treatment. In the collaborative project described in Chapter 5, no systematic exclusions were identified in any of the three studies. The PSD and NSHPC were comprehensive and aimed to include all births to HIV-infected women identified within the defined study area. The ECS was based in specific centres and required enrolment, but very high enrolment rates were

reported, with no systematic exclusions due to refusal or to late presentation or diagnosis (Patel, 2007).

The PSD and ECS were based in specific hospitals and clinics, and the populations covered may not have been totally representative of the wider population of HIV-infected pregnant women. In fact, the PSD was set up specifically to cover areas of high HIV prevalence. However, this is unlikely to have led to bias in the association between ART exposure and prematurity, since in most cases neither administration of treatment nor delivery had occurred at the time of inclusion in the study. Some women were already on treatment before pregnancy, but as shown for the NSHPC, most were on HAART (95%) (information on timing of treatment initiation was not available for the PSD). Overall, no specific methodological factors relating to inclusion criteria or case ascertainment were identified which would have led to the observed heterogeneity between studies.

Population differences

There were broad population differences between studies, as shown by variation in the prevalence of IDU, ethnic group and other demographic characteristics, which has also been highlighted elsewhere (Newell *et al.*, 2007). Baseline prematurity rates also differed, ranging from 12% in the NSHPC, to 15% in the ECS, and 17% in the PSD. In the US, rates have traditionally been higher than in other developed countries, at 10-12% (Institute of Medicine, 2006), compared with 5-9% in Europe and other developed countries including the UK (Aveyard *et al.*, 2002; Gardosi & Francis, 2000; Goldenberg *et al.*, 2008; Tucker & McGuire, 2004). However, in the analysis presented in Chapter 5, the association between treatment and prematurity was measured using odds ratios, and multiplicative effects should therefore not be affected by differences in baseline prevalence (Kirkwood & Sterne, 2003). In fact, a

higher baseline prematurity rate would mean smaller numbers of pregnancies would be required to detect an effect of the same relative magnitude.

Type of ART varied between studies, as did the drugs included within regimens. Although detailed information on drugs included within HAART regimens was not available, differences between populations were apparent, with PI-based HAART more commonly used in the PSD and ECS, and non-PI-based HAART more common in the NSHPC up to 2002. There was some variation in dual therapy regimens, but in all three studies dual regimens consisted predominantly (over 70%) of zidovudine and lamivudine. Monotherapy consisted almost entirely of zidovudine. Since heterogeneity was mainly apparent in the comparison of HAART with monotherapy, but not with dual therapy, it is unlikely that differences between studies were due to differences in specific regimens. No difference in prematurity rates between PI and non-PI HAART was observed in any of the studies. Furthermore, the suggested biological mechanism for the HAART-prematurity association relates to the overall effect of combination therapy on the cytokine environment (Fiore *et al.*, 2006).

Analytical approach

One of the difficulties in comparing studies of ART and pregnancy outcome is the definition and selection of treatment groups. In some studies combination therapy consisted of two or more antiretroviral drugs (Mandelbrot *et al.*, 2001), while in others it referred to three or more (European Collaborative Study and the Swiss Mother + Child HIV Cohort Study, 2000). The choice of comparison groups also differed, with monotherapy and dual therapy combined in some studies (European Collaborative Study, 2004a), but not in others (Schulte *et al.*, 2007). In this analysis, the same comparison group (monotherapy) was chosen for all three studies, and

significant heterogeneity in the association between HAART and prematurity was apparent. However, there were some similarities in the pattern of prematurity by ART; in all three studies, rates were lowest in women on dual therapy, higher in those on monotherapy, and higher again in untreated women (Figure 5.7, page 186). However, in the ECS and NSHPC, the rate in women on HAART was higher than in those on monotherapy or dual therapy, while in the PSD, this rate was similar to those on monotherapy, but higher than in those on dual therapy. If dual therapy was used as a baseline, there was no significant heterogeneity in the association with prematurity, and unadjusted odds ratios ranged from 1.25 (PSD) to 1.80 (ECS). Pooling the data and adjusting for study yielded a significant 1.5-fold increase in prematurity associated with HAART, which remained after adjusting for ethnic group, region of birth, IDU, year of delivery, and clinical status. The choice of baseline did, therefore, affect the findings, leading to different conclusions about the association between HAART and prematurity. In the PSD, choosing monotherapy as a baseline resulted in there being no association between HAART and prematurity, while choosing dual therapy resulted in a significant association. In light of the consistency between the ECS and NSHPC with monotherapy as a reference category, and the consistency across the three studies with dual therapy as a baseline, HAART appears to be associated with a significantly increased risk of prematurity.

Confounding and bias

The three studies included in this project were chosen in part because of a history of successful collaboration and data sharing between the study groups. Although there were similarities in the data collected, some variables were not available in all of the studies, and it was not possible to control for certain risk factors consistently. In particular, since the PSD was a paediatric study, certain maternal variables (age, CD4

count and viral load) were not collected. Furthermore since none of the three studies were specifically set up to monitor ART and pregnancy outcome, information was only available on some of the known risk factors for prematurity, and there were differences between studies in what information was collected, and in how risk factors were measured (Chapter 5, Table 5.9).

Although IDU was included in the analyses, the quality of information varied between studies. In the NSHPC, IDU was reported as the route of HIV acquisition, and did not necessarily reflect current IDU. Although there may have been some misclassification, it is unlikely that it would be related to ART. Misclassification would therefore tend to attenuate the association between ART and prematurity, because the decline over time in both monotherapy and IDU meant that in all three studies, women classified as IDU were more likely to be on monotherapy than on HAART (data not shown). Adjusting for IDU (along with ART, ethnic group, region of birth and year) led to an increase in the odds ratio for the effect of ART on prematurity in the ECS and NSHPC, suggesting some confounding by IDU, but this was not the case in the PSD. Misclassification of IDU in the PSD may have concealed an association between HAART and prematurity. Information on use of other illicit substances in pregnancy was not available, but is likely to have differed between studies. If, like IDU, use of other illicit drugs was associated with monotherapy, the inability to adjust for this in the PSD could also have masked an association between HAART and prematurity when monotherapy was used as a comparison group.

Maternal age was not routinely available in the PSD; however, in a small subset of women, median maternal age was not substantially different from that in the ECS and NSHPC. Furthermore maternal age was not significantly associated with

prematurity in the ECS or NSHPC, and it is therefore unlikely that the inability to adjust for age in the PSD substantially altered the findings.

The ethnic profile of the populations varied substantially between studies; there were differences not only in the proportion of black and white women, but also within these broad ethnic categories, which were not comparable across studies. In the PSD most black women were US-born (i.e. 'African American'), whereas in Europe the majority of black women were born in sub-Saharan Africa and had arrived in Europe relatively recently (as shown in Chapter 3 for the NSHPC). Considering these differences, it is not surprising that the association between ethnic group and prematurity was not consistent across studies; in fact, in multivariable analysis ethnic group was only associated with prematurity in the PSD, with black women about 50% more likely than white women to deliver prematurely. Ethnic differences in preterm delivery rates have been reported for the wider US population (Institute of Medicine, 2006). Observed ethnic differences in prematurity rates in the PSD could therefore be due to socio-economic factors or disparities in access to healthcare (Blustein, 2008). Nevertheless, adjusting for ethnic group in the PSD did not substantially alter the association between ART and prematurity, and there were no significant interactions between ethnicity and ART after adjusting for other factors. In all three studies, mothers who were born abroad had a lower risk of premature delivery than those born within the study region, although this was not statistically significant in the ECS or NSHPC. In the US, foreign-born adults fare considerably better than those born in the US in terms of a number of health outcomes (including obesity, cardiovascular disease and pregnancy outcomes, such as preterm delivery and low birth weight), despite limited access to healthcare and adverse social circumstances (Dey & Lucas, 2006; Reed *et al.*, 2005). Furthermore, among

immigrant groups, length of stay in the US is associated with a deterioration in health measures, including prematurity and low birth weight (Callister & Birkhead, 2002; Dey & Lucas, 2006). Social support, diet and low rates of smoking and alcohol consumption may play a role (Page, 2004).

Information on other risk factors for prematurity, such as low socio-economic status, smoking, sexually-transmitted infections, and prior preterm delivery (Slattery & Morrison, 2002) was not collected in the PSD, ECS or NSHPC, and the prevalence of these risk factors is likely to have differed between studies. In a secondary analysis of an international MTCT clinical trial involving HIV-infected pregnant women, US women were more likely than European women to have a history of sexually-transmitted infections, as well as previous pregnancies and miscarriages (Newell *et al.*, 2007). Any trends over time in these risk factors would produce an association between those factors and treatment, since the latter also varied over time. In the PSD the majority of pregnancies in women on monotherapy occurred before 2000, when IDU and HIV-related symptoms were more common and monotherapy was used more widely than in recent years. In contrast, in the NSHPC the dramatic increase in the number of pregnancies since 2000 and continued use of monotherapy has meant that the majority of monotherapy exposures occurred during the HAART era. The comparison between HAART and monotherapy was therefore more historical in the PSD (and in the ECS) than in the NSHPC. A decline over time in unmeasured risk factors for prematurity could have led to an attenuation of the association between HAART and prematurity, which may have been accounted for to some extent, although not fully, by the inclusion of year of delivery in the models.

On the other hand, selection bias in terms of allocation to treatment groups may have been a more important methodological concern in the NSHPC than in the other two

studies. Since none of the studies were randomised with respect to treatment, decisions about type of ART would have been made on the basis of availability of regimens, local and national treatment guidelines, and clinical indication, all of which would have varied between studies. Differences in the use of ART between the three studies were apparent: dual therapy was more widely used in the PSD than in the ECS or NSHPC, and monotherapy was less common in recent years in the PSD. It has been suggested that selective use of more potent treatments for women with more advanced HIV disease could explain the difference in prematurity rates in different treatment groups (Tuomala & Yawetz, 2006). However, since the advent of HAART, US treatment guidelines have been more cautious than European ones toward use of monotherapy for preventing MTCT, and now recommend it only be considered for women with viral loads <1000 copies/ml, compared with <6000-10,000 copies/ml in current British guidelines (BHIVA/CHIVA, 2008; Coll *et al.*, 2002; Perinatal HIV Guidelines Working Group, 2008). This would suggest that when comparing HAART and monotherapy in recent years, selection bias would be more likely in the PSD than in the ECS or NSHPC. There was no evidence of this in these analyses, although an association could have been masked by concurrent changes in maternal characteristics.

Adjusting for clinical status, CD4 cell count and HIV RNA viral load did not substantially alter the association between ART and prematurity, despite the fact that all three were significantly associated with prematurity. Although adjusting for these factors would not necessarily remove all bias introduced by indication for treatment, it is likely that if substantial bias were present, adjusting for factors related to it would reduce the magnitude of the association; in fact, controlling for these variables increased the association between ART and prematurity in both the ECS and the

NSHPC. The inability to adjust for CD4 count and/or viral load in the PSD meant that the possible confounding effects of indication for treatment were addressed to a lesser extent in this study (only through the inclusion of clinical status). It was also not possible to adjust for repeat pregnancies in the PSD, another factor which led to an increase in the odds ratios for prematurity in the ECS and NSHPC.

An important limitation in this analysis was the inability to adjust for certain potential confounders, which could affect the findings in all three studies, but particularly in the PSD, in which maternal and pregnancy information was more limited. It is possible that the lack of association between HAART (versus monotherapy) and prematurity in the PSD could have been due to unmeasured confounding, since the comparison between the two groups in the PSD was more historical (i.e. most monotherapy exposures occurred pre-2000, and most HAART exposures since 2000). However, this explanation is not consistent with the fact that a greater association between HAART and prematurity was estimated in the ECS (AOR=2.9) than in the NSHPC (AOR=1.5), despite the HAART-monotherapy comparison being more historical in the ECS than in the NSHPC.

Conclusions

The PSD differed substantially from the ECS and NSHPC in the association between ART and premature delivery, when comparing HAART and monotherapy. Despite the identification of population and methodological differences, and the use of a standard analytical approach, no clear explanation for these conflicting findings was identified in this comparative analysis. However, it is possible that the inability to adjust for maternal viral load and CD4 cell count, or for repeat pregnancies, could have attenuated the association between HAART and prematurity in the PSD. There was no heterogeneity in terms of the HAART-prematurity association when dual

therapy was selected as a baseline; in this separate analysis, HAART was associated with a significantly increased risk of prematurity in all three studies.

Although a randomised control trial of ART in pregnancy is not feasible, a carefully designed cohort study could potentially address some of the limitations of these studies, providing detailed information was collected on other risk factors for premature delivery, on clinical factors including CD4 count and viral load before and after initiation of treatment, and on type and timing of ART in pregnancy. However, to carry out full multivariable analyses in any such study would require larger numbers of pregnancies than those currently available.

7.5 Risks and benefits of antiretroviral therapy in terms of pregnancy outcome

Much of the focus in this thesis has been on exploring adverse outcomes associated with ART. Although it is important to be aware of the risks associated with treatment, these must be considered in relation to the benefits for any conclusions about the value of the treatment to be made. In Chapter 6, a risk-benefit model was developed to enable the observed risks of prematurity and stillbirth to be quantified in relation to the main benefit of treatment, a reduction in the risk of MTCT. Comparison was made between HAART (any time) and monotherapy in the pre-HAART era, since use of monotherapy in more recent years has been restricted to women with relatively low viral load, who therefore have a lower baseline risk of transmission. This comparison enabled the full extent of the benefits associated with HAART to be quantified in the context of the reported risks.

The models suggested that avoiding 100 transmissions through exclusive use of HAART would result in an additional 68 infants born at <37 weeks, including 23 born at <32 weeks, and 10 additional stillbirths, compared with exclusive use of monotherapy. Confidence intervals around the three estimates approached or crossed zero, and were therefore borderline or non-significant for all three outcomes. In these models, altering the risk of MTCT according to prematurity to allow for an increased risk of transmission in premature infants did not affect the results. These findings relate to a population level approach, where either monotherapy or HAART was used; although the models showed no difference between the exclusive HAART scenario and the selective monotherapy scenario, for individual women who do not require HAART for their own health, the option of minimising the risk of prematurity and stillbirth with no additional increase in the risk of transmission would clearly be optimal.

Interpretation of the results of these risk-benefit models depends on the relative severity of the risks and benefits. In absolute terms, HAART would be considered superior to exclusive monotherapy, since more infants are prevented from becoming infected than are born premature or stillborn. However, further information is required in order to determine an appropriate risk-benefit acceptability threshold for these outcomes. Prematurity is associated with a significantly increased risk of perinatal morbidity and mortality, although this is generally confined to infants born very prematurely (Saigal & Doyle, 2008). On the other hand, HIV infection has serious lifelong consequences, including a considerable annual risk of progression to AIDS and death. However, it is now treatable, and prognosis for HIV-infected children has increased substantially over the last decade since the introduction of effective ART (Judd *et al.*, 2007). Furthermore, the appropriate balance of

prematurity and MTCT is likely to vary by population and healthcare setting. In countries with poor health systems, both prematurity and HIV will be associated with higher rates of morbidity and mortality than in resource-rich settings, and the relative consequences and costs of the different outcomes will vary according to the quality of neonatal care facilities and availability of ART. Population-specific information on outcomes in premature infants and HIV-infected children would ideally be factored into decisions regarding the acceptable risk-benefit threshold. Additionally, the possibility that ART-exposed premature infants experience improved outcomes compared with infants born prematurely for other reasons (European Collaborative Study, 2004c) would also need to be considered. Finally, attitudes and preferences of both clinicians and patients towards the acceptability of different perinatal outcomes, which may be affected by the continued stigma of HIV (Anderson & Doyal, 2004; Bunting, 1996), may also influence decision-making with regards to ART-related risks and benefits. Further information on mortality, morbidity and longer-term outcomes, as well as their associated costs, for both HIV-infected and premature children would enable a more informed assessment of the acceptability of the ratio of risks to benefits estimated in this analysis.

7.6 Strengths and weaknesses of NSHPC surveillance data

The NSHPC is an active reporting system with high response rates: over 90% of respondents routinely return the quarterly notification card (www.nshpc.ucl.ac.uk). Through this study, information is sought on all HIV-infected pregnant women diagnosed any time up to delivery throughout the UK and Ireland, regardless of maternal characteristics or uptake of interventions. Comparison of the number of pregnancies reported to the NSHPC with national unlinked anonymous

seroprevalence data suggests that case ascertainment for pregnancies in HIV-infected women ending in a live birth is extremely high: over 95% in 2007 (Health Protection Agency, 2008). Since a small proportion of infected women remain undiagnosed at delivery, ascertainment of diagnosed women is likely to be even higher, thanks to the active and complementary nature of the obstetric and paediatric reporting schemes. About 20% of births were reported through only one of the schemes; the parallel approach therefore ensures a higher ascertainment rate than would be achievable through a single scheme. Despite the complementary nature of the schemes, it was not possible to estimate the likely proportion of missed cases by capture-recapture methods, since the two schemes are not independent. When pregnancies are notified, missing paediatric reports are routinely followed up, and vice versa.

Although high coverage rates are achieved through the NSHPC, this can only be accomplished with the cooperation of a large number of health professionals. About 240 obstetric respondents, in most cases one for each maternity unit, are currently involved in the study (see www.nshpc.ucl.ac.uk), while almost 3000 paediatricians report to the British Paediatric Surveillance Unit's Orange card system (BPSU, 2008), about 130 of whom notified cases to the NSHPC in 2005 (NSHPC unpublished data). Because of the number of respondents involved, and in the interests of maintaining high response rates, there were naturally limits on the amount and type of data that could be collected, and information on certain potentially relevant confounders was not available.

Although considerable effort went into ensuring that missing information was kept to a minimum, some was inevitable. Often this was random – for example, if a respondent accidentally skipped a question – but in some cases, patterns to the missing data were apparent. Where information was missing on a particular exposure

or outcome, details of other characteristics were sometimes more likely to have been omitted, owing to a common underlying cause. For instance, late presentation for antenatal care or unexpected premature delivery may have resulted in limited maternal details being collected, as well as insufficient time for running routine laboratory investigations. Where cases were reported through only one branch of the surveillance scheme (obstetric or paediatric), information on all variables collected only through the other scheme were inevitably missing. Patterns in missing data were also caused by changes over time in guidelines or protocols, such as viral load testing in pregnancy. The effects of excluding cases with missing data differed for each analysis, and were therefore discussed in the relevant sections of this thesis.

In most analyses, comparison was made between different treatment groups. Identifying an appropriate group of uninfected controls was not feasible, particularly given the substantial differences in demographic characteristics between HIV-infected women and the general population.

7.7 Conclusions and implications for clinical management

This thesis describes the changing epidemiology of HIV in pregnancy in the UK and Ireland, and highlights the success of routine antenatal HIV screening policies, both through increased detection of HIV in pregnancy and high uptake of antiretroviral therapy, leading to very low mother-to-child transmission rates: only 1.2% in 2000-2006. A range of strategies for the management of HIV in pregnancy are now available (BHIVA/CHIVA, 2008), and most women are recommended and receive HAART in pregnancy. Nevertheless, zidovudine monotherapy with planned caesarean section remains an alternative for women who do not require HAART for

their own health, and is supported by these findings, showing no transmissions among over 450 women opting for this approach. The more tolerant approach towards vaginal delivery for women who achieve full viral suppression on HAART was evident in these findings, with rates of planned vaginal delivery rising over time. These data also support this management approach, with transmission rates in women opting for HAART and planned vaginal delivery not significantly higher than with elective caesarean section. These findings must, however, be interpreted in the context of current guidelines, in which interventions are recommended on the basis of timing of maternal diagnosis, clinical presentation, response to treatment, and other individual factors.

These low transmission rates in diagnosed women highlight the importance of ensuring that women are identified as HIV-infected in time to take up appropriate interventions; early testing for all pregnant women should remain a priority. Continuing to improve the offer and uptake of antenatal HIV testing could have a significant impact on further reducing MTCT, since most perinatally acquired infection is now among infants whose mothers remain undiagnosed at delivery (AIAU, NSHPC, & CHIVA, 2007).

The potential for adverse outcomes associated with treatment is an important consideration for HIV-infected pregnant women, particularly those who do not require treatment for their own health. These findings support the premise that HAART in pregnancy is associated with an increased risk of premature delivery and possibly stillbirth. The number of births to diagnosed HIV-infected women in the UK and Ireland continues to rise, and an increasing number of women are on treatment at conception. Being on HAART in early pregnancy was not associated with an increased risk of congenital abnormalities, but was associated with a possible

increase in the risk of pre-eclampsia. Monitoring adverse pregnancy and perinatal outcomes should remain a priority, and further research into the mechanisms leading to pre-eclampsia, premature delivery and stillbirth in HIV-infected women is needed.

Questions remain regarding the acceptable balance of risks and benefits associated with different treatment approaches. While HAART provides overall benefits, it seems appropriate to offer monotherapy to women who do not yet require HIV treatment for their own health, since this approach will minimise the risk of adverse outcomes. Earlier initiation of treatment is likely to reduce the risk of *in utero* transmission, which accounts for an increasing proportion of perinatal transmissions (Warszawski *et al.*, 2008), and may cut overall transmission rates to below 1%. Latest guidelines now suggest starting HAART prior to fetal viability (24 weeks), or as early as 20 weeks if a woman has high baseline viral load and wishes to deliver vaginally (BHIVA/CHIVA, 2008). In risk-benefit analyses, it was not possible to compare scenarios involving differential timing of initiation of treatment, and indeed the number of transmissions in these groups would be too small to yield conclusive results.

In conclusion, analysing data from ongoing prospective surveillance of HIV in pregnant women has enabled the impact of changes in guidelines and clinical practice on the uptake and effectiveness of interventions to be assessed, and has provided timely evidence on mother-to-child transmission rates as well as adverse outcomes.

7.8 Future work

Mother-to-child transmission

With MTCT rates now very low, remaining questions relating to transmission become increasingly difficult to answer as larger numbers of pregnancies are required to achieve sufficient statistical power. As many of the risk factors for MTCT have been identified, and can be minimised, remaining cases of perinatal transmission are increasingly attributable to a range of complex social and management issues (AIAU, NSHPC, & CHIVA, 2007). Detecting patterns relating to other preventable factors is challenging, and may require collaboration between different study groups. Information on duration of ruptured membranes is now being collected through the NSHPC. However, although vaginal deliveries in women with undetectable viral load have increased in recent years, it is not clear whether many women are allowed to remain undelivered several hours after membranes have ruptured, since current guidelines advocate "a low threshold for caesarean section in the face of slow or difficult labour or concern about fetal condition" (BHIVA/CHIVA, 2008). In any case, a large number of pregnancies will be required to answer this question, and as with other remaining questions around MTCT, a collaborative approach is more likely to produce answers than a single study.

Adverse maternal and pregnancy effects of antiretroviral therapy

These analyses contribute to the debate about the association between ART and pregnancy outcome, particularly prematurity. As mentioned previously, a carefully designed cohort study could potentially overcome some of the limitations inherent in these surveillance data and in other studies, such as issues around indication for

treatment and other prematurity risk factors. However, an entirely new study to address this question would not, at this stage, be an appropriate use of resources, given the current body of evidence, the balance of risks and benefits demonstrated in Chapter 6, and the large sample size required.

Further research into the relationship between HIV, ART and the cytokine environment during pregnancy could provide useful information, not only on the biological plausibility of the link between HAART and preterm delivery, but also on the immunological mechanisms underlying other pregnancy complications, such as pre-eclampsia and stillbirth, which seem to be increased in ART-treated women. Information on risk factors for HAART-associated preterm delivery is also needed, to enable early identification of 'at risk' women, and targeted management of these pregnancies.

Further investigation into the safety of zidovudine monotherapy in terms of longer-term maternal outcomes such as future drug resistance would enable this approach to be recommended more confidently for women not requiring HAART, thereby minimising overall fetal exposure to antiretroviral drugs. Such information would also be relevant for African populations, where zidovudine monotherapy is used more widely in combination with single-dose nevirapine at delivery. Questions remain about the effect of postpartum treatment interruption, such as following zidovudine monotherapy in pregnancy, on maternal disease progression. These questions are currently being investigated in a cohort of HIV-infected women followed up after pregnancy in the Ukraine (C Thorne, personal communication, 2009).

Development of risk-benefit models

The models presented in Chapter 6 provided ratios of risks to benefits which suggested that despite the associated risks, exclusive HAART was overall more favourable than exclusive monotherapy. Optimal risk-benefit acceptability thresholds could be estimated quantitatively, based on cost and/or mortality data for both sets of outcomes, which could be obtained from the existing literature. These models could also be developed for use in other populations or for different scenarios or adverse outcomes, which were not addressed in this thesis; in a recent study, the risks of mitochondrial toxicity associated with a number of different ART regimens were compared with the benefits in a decision analysis model (Ciaranello *et al.*, 2008). Best and worst case scenarios were derived, and sensitivity analyses were used to examine the effect of varying relevant parameters. The benefits of Monte Carlo methods for this type of analysis are that risk-benefit ratios are obtained, which facilitate comparison across groups, and that realistic confidence intervals can be derived. The estimates used in these models were all obtained from NSHPC data. In order to make the findings more generalisable, summary estimates drawing on a number of published studies could instead be used as inputs to the models.

Monitoring for adverse outcomes in exposed children

Finally, continued widespread use of potent combinations of antiretroviral drugs in pregnancy means that monitoring of ART in pregnancy and perinatal life is essential to ensure that any further adverse effects in exposed children are detected and quantified early on. Concerns have already been raised regarding haematological changes (European Collaborative Study, 2004b; Le Chenadec *et al.*, 2003; Sperling *et al.*, 1998), mitochondrial toxicity (Barret *et al.*, 2003) and the potential for malignancies (Olivero *et al.*, 2002). New drugs and drug classes are appearing

regularly, and the number of possible combinations of drugs is rising rapidly; each new drug and new regimen may be associated with risks to the fetus or mother. Prospective surveillance at a national level has provided invaluable information about the extent of these exposures, as well as their associated risks. While many questions around HIV and pregnancy have at least in part been answered, the emphasis is shifting towards addressing continued safety concerns in a sustainable way. Children born to HIV-infected women in the UK are now being 'flagged' through the Office for National Statistics for death and cancer registrations, allowing these more serious outcomes to be routinely monitored (Hankin *et al.*, 2007). In the future, it may be possible to extend this data linkage protocol to include more routine hospital records, which would enable monitoring of other potential adverse outcomes, including longer-term ones (Barret *et al.*, 2003; European Collaborative Study, 2005c), associated with *in utero* exposure to antiretroviral drugs.

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Appendix 1 Publications and conference abstracts arising from this research

List of publications

Original papers	Reprint page	Thesis chapter
Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. AIDS 2009; 23(4): 519-24.	333	4
Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA**.** Trends in management and outcome of pregnancies in HIV infected women in the United Kingdom and Ireland, 1990-2006. *BJOG* 2008; 115(9): 1078-1086.	339	3
Townsend CL, Cortina-Borja M, Peckham CS, De Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* 2008; 22(8): 973-981.	348	3
Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS* 2007;21: 1019-26.	357	5
Townsend CL, Tookey PA, Cortina-Borja M and Peckham CS. Antiretroviral therapy and congenital abnormalities in infants born to HIV-1 infected women in the United Kingdom and Ireland, 1990-2003. *JAIDS* 2006; 42 (1): 91-94.	365	4
Correspondence		
Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Response to Kourtis et al 'Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis' [Correspondence]. *AIDS* 2007, 21: 1831–1832.	369	5

List of conference abstracts

Townsend CL, Tookey PA, Cortina-Borja M. Premature delivery and mother-to-child transmission: risks and benefits of HAART in pregnancy. 16th Conference on Retroviruses and Opportunistic Infections (CROI), Montreal, Canada, 8-11 February 2009. Abstract 927. *(Poster)*

Townsend CL, Schulte J, Thorne C, Dominguez K, Cortina-Borja M, Peckham CS, Tookey PA, Bohannon B, Newell M-L. Differences in the association between HAART in pregnancy and premature delivery: a comparison of three studies in the United States and Europe. XVII International AIDS conference. Mexico City, 3-8 August 2008. *(Poster)*

Townsend CL, Cortina-Borja M, Peckham CS, Lyall H, de Ruiter A, Tookey PA. Very Low Risk of Mother-to-Child Transmission (MTCT) in Women on HAART Who Achieve Viral Suppression: Data from the United Kingdom and Ireland, 2000-2006. Royal College of Paediatrics and Child Health 12th Spring Meeting, York, UK, 14-17 April 2008. *Archives of Disease in Childhood* 2008; 93(suppl_1):A3-A4. Abstract P6. (*Oral presentation)*

Willey BA, Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Congenital abnormalities and *in utero* exposure to antiretroviral therapy in the UK and Ireland. Royal College of Paediatrics and Child Health 12th Spring Meeting, York, UK, 14-17 April 2008. *Archives of Disease in Childhood* 2008; 93(suppl_1): A75-A84. Abstract ALL/THUR/24. (*Oral presentation)*

Townsend CL, Schulte J, Thorne C, Dominguez K, Cortina-Borja M, Peckham CS, Tookey PA, Newell M-L. Differences in the association between ART in pregnancy and premature delivery: a comparison of three studies in the United States and Europe. 12th International Workshop on HIV Observational Databases, Malaga, Spain, 27-30 March 2008. Abstract 65. *(Poster)*

Townsend CL, Cortina-Borja M, Peckham CS, Lyall H, de Ruiter A, Tookey PA. Very Low Risk of Mother-to-Child Transmission (MTCT) in Women on

HAART Who Achieve Viral Suppression: Data from the United Kingdom and Ireland, 2000-2006. 15th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, 3-6 February 2008. Abstract S-108. Poster #653.

Townsend CL, Masters J, Tookey PA. Surveillance of HIV infection in pregnant women in the United Kingdom and Ireland, 1990-2006. Health Protection 2007, Warwick University, 17-19 September 2007. *(Oral presentation)*

Townsend CL, Masters J, Peckham CS, Tookey PA. Vertically acquired HIV infection in the UK and Ireland in the era of routine antenatal testing (2000-2005). Royal College of Paediatrics and Child Health 11th Spring Meeting, York, UK, 2007. *Archives of Disease in Childhood* 2007;92(suppl_1):A80-A87. Abstract G/THUR/ALL6. (*Oral presentation)*

Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Premature delivery, vertical transmission and antiretroviral therapy in HIV-infected pregnant women in the UK and Ireland. 11th International Workshop on HIV Observational Databases. Monte Carlo, 22-25 March 2007. (*Oral presentation)*

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Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Premature delivery in women receiving HAART: data from national HIV surveillance in the UK and Ireland, 1990-2005. Health Protection 2006, Warwick, 11-13 September 2006. *(Oral presentation)*

Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Prematurity and antiretroviral therapy: population-based HIV surveillance in the UK and Ireland, 1990-2005. XVI International AIDS conference. Toronto, 13-18 August 2006. Abstract MOPE0532. (*Poster)*

Townsend CL, Masters J, Tookey PA. Surveillance of HIV infection in pregnant women in the United Kingdom and Ireland, 1990-2004. 10th International Workshop on HIV Observational Databases. Madrid, 23-26 March 2006. Abstract 40. (*Poster)*

Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990–2007

Claire L. Townsend, Barbara A. Willey, Mario Cortina-Borja, Catherine S. Peckham and Pat A. Tookey

Objective: To explore the rate of reported congenital abnormalities in infants exposed to antiretroviral therapy *in utero*.

Design: Comprehensive national surveillance study in the UK and Ireland.

Methods: Births to diagnosed HIV-infected women are reported to the National Study of HIV in Pregnancy and Childhood. Infants born between 1990 and 2007 were included.

Results: The rate of reported major and minor congenital abnormality was 2.8% (232/8242) overall, and there was no significant difference by timing of ART exposure: 2.8% (14/498) in unexposed infants, 2.7% (147/5427) following second or third trimester exposure, and 3.1% (53/1708) following first trimester exposure ($P = 0.690$). There was no difference in abnormality rates by class of ART exposure in the first trimester ($P = 0.363$), and no category of abnormality was significantly associated with timing of ART, although numbers in these groups were small. There was no increased risk of abnormalities in infants exposed to efavirenz ($P = 0.672$) or didanosine ($P = 0.816$) in the first trimester.

Conclusion: These findings, based on a large, national, unselected population provide further reassurance that ART *in utero* does not pose a major risk of fetal anomaly.

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Keywords: antiretroviral therapy, congenital abnormalities, HIV, pregnancy, United Kingdom

Introduction

Antiretroviral therapy (ART) has had a major impact on reducing the risk of mother-to-child transmission of HIV [1], and the majority of HIV-infected women in the UK and Ireland now receive ART at some time in pregnancy [2]. Nevertheless, there are concerns about potential teratogeneticity, particularly since around a quarter of HIV-infected women conceived on treatment in recent years [1].

Large-scale observational studies have so far detected no overall increase in congenital abnormality rates associated with first trimester ART exposure [3–5]. However, an

MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, London, UK.
Correspondence to Claire L. Townsend, MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK.
Tel: +44 20 7905 2336; fax: +44 20 7905 2381; e-mail: c.townsend@ich.ucl.ac.uk
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increased abnormality rate in 353 infants exposed to didanosine in the first trimester [4.5%, 95% confidence interval (CI) 2.6–7.3%] compared with a population rate of 2.7% was recently detected through international prospective monitoring by the Antiretroviral Pregnancy Registry [6], and a significantly increased prevalence of hypospadias following first trimester zidovudine exposure (7/382), compared with later or no exposure (2/892), has been reported from the Women and Infants Transmission Study (WITS) [4]. There have also been case reports of neural tube defects in infants exposed to efavirenz in the first trimester [7,8].

HIV infection in pregnant women and their children has been monitored in the UK and Ireland since the late 1980s, through a unique, population-based surveillance scheme [2]. We previously investigated the association between in-utero ART exposure and congenital abnormalities in over 3100 infants born between 1990 and 2003 [9]. In this updated analysis, including four additional years of surveillance data, we report on over 8500 children born between 1990 and 2007.

Methods

Active surveillance of obstetric and pediatric HIV in the UK and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC). Full methods are described elsewhere [1,2]. This analysis includes all infants (live born, stillborn, twins and triplets) born between 1990 and 2007 in the UK and Ireland to women diagnosed before delivery, and reported by June 2008. Information on maternal demographic characteristics, pregnancy outcome, delivery, perinatal details, type and timing of ART is routinely collected through the NSHPC. Congenital abnormalities are reported by both obstetric and pediatric respondents, mostly within the first few weeks of life. Most variables are obtained from both sources, except for timing of ART and maternal clinical status (AIDS or HIV-related symptoms in pregnancy), which are collected only from obstetric respondents.

Timing of ART exposure in pregnancy was classified as early if therapy was started before conception or up to 12 completed weeks of gestation, and late if started after 12 weeks. Class of antiretroviral regimen was categorized as nucleoside reverse transcriptase inhibitors (NRTIs) only, or according to inclusion of nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, or both NNRTIs and protease inhibitors. Four infants in the protease inhibitor group were also exposed to fusion inhibitors in the first trimester (none had an abnormality reported).

Congenital abnormalities were classified using the World Health Organisation's International Classification of Diseases [10]. For infants with multiple abnormalities reported ($n=19$), only the main abnormality was included in the analysis. Detailed information on whether abnormalities were major or minor was not routinely collected; however, in order to assess the prevalence of major abnormalities, the following were classified as minor: polydactyly, malformed ear, abnormalities of the feet, minor mouth abnormalities, undescended testes, accessory nipple, spinal hairy patch, strawberry nevi, skin tag, and subclinical sub-ependymal cysts.

Data were managed in a Microsoft Access 2002 database and analyzed using Stata 10.0 (Stata Corporation, College Station, Texas, USA). Congenital abnormality rates and 95% CIs were calculated. Because of specific concerns, abnormality rates were also calculated for infants exposed to efavirenz or didanosine in early pregnancy, as was the rate of hypospadias in male infants. Differences in rates were assessed using χ^2 and Fisher's exact tests. Logistic regression models were developed to adjust for potential confounders, including maternal ethnicity, age, injecting drug use (as the reported route of HIV acquisition) and clinical status [11].

Results

Maternal and pregnancy characteristics and antiretroviral therapy

Altogether 8576 infants were reported, including 92 stillbirths and 288 twins or triplets. Information was available from both pediatric and obstetric sources for 79% of infants, but the remainder were reported only through the obstetric (10%) or pediatric (11%) scheme. Information on congenital abnormality was available for 96.1% (8242/8576) of infants. Of these, most were born between 2000 and 2007 (Table 1). Three-quarters were born to black African women, and median maternal age at delivery was 30 years [interquartile range (IQR) 26.3–33.8 years]. Median age at last report was 6 months (IQR 3–15 months).

Information on timing of ART exposure was missing for 7.4% (609/8242) of infants, mostly (88%, 538/609) because reports were only obtained from pediatric respondents who were not asked to provide this information. Less than a quarter of infants (22.4%) had early in-utero exposure (Table 1), mostly to NNRTI-containing regimens (52.9%).

Congenital abnormalities

Altogether 232 infants out of 8242 were reported to have at least one congenital abnormality (2.8%, 95% CI 2.5–3.2%), a quarter of whom had only minor abnormalities (59/232). The abnormality rate excluding minor defects was 2.1% (95% CI 1.8–2.4%). Infants with missing information on congenital abnormality ($n=334$) were

Table 1. Risk factors for congenital abnormalities in 8242 infants; rates and unadjusted odds ratios.

	Total		Congenital abnormality		Unadjusted odds ratios		
	n	%	*n*	%	Odds ratio	95% confidence interval	*P*
Time period ($n=8242$)							
≤1999	833	10.1	31	3.7	1.00		
2000–2007	7409	89.9	201	2.7	0.72	0.49–1.06	0.970
Maternal characteristics							
Ethnic origin ($n=8171$)							
White[a]	1285	15.7	46	3.6	1.00		
Black African[b]	6244	76.4	162	2.6	0.72	0.51–1.00	0.051
Black Other	326	4.0	13	4.0	1.12	0.60–2.10	0.726
Other	316	3.9	10	3.2	0.88	0.44–1.76	0.719
Age at delivery ($n=8184$)							
<25 years	1471	18.0	40	2.7	1.00		
25–34 years	5154	63.0	147	2.9	1.05	0.74–1.50	0.786
≥35 years	1559	19.0	43	2.8	1.01	0.66–1.57	0.948
HIV exposure group ($n=8242$)							
Other risk[c]	7876	95.6	219	2.8	1.00		
Injecting drug use	366	4.4	13	3.6	1.29	0.73–2.28	0.384
Clinical status ($n=7235$)							
No HIV-related symptoms	6451	89.2	174	2.7	1.00		
HIV-related symptoms/AIDS	784	10.8	32	4.1	1.54	1.05–2.25	0.029
Infant characteristics							
Sex ($n=8202$)							
Male	4123	50.3	137	3.3	1.00		
Female	4079	49.7	91	2.2	0.66	0.51–0.87	0.003
Gestational age ($n=8056$)							
≥37 weeks	6874	85.3	182	2.6	1.00		
<37 weeks	1182	14.7	47	4.0	1.52	1.10–2.11	0.012
Birth weight ($n=7153$)							
≥2.5 kg	6067	84.8	158	2.6	1.00		
<2.5 kg	1086	15.2	45	4.1	1.62	1.15–2.27	0.005
Treatment characteristics							
Timing of antiretroviral therapy exposure ($n=7633$)							
Not treated in pregnancy	498	6.5	14	2.8	1.00		
Late (second/third trimester)	5427	71.1	147	2.7	0.96	0.55–1.68	0.893
Early (first trimester)	1708	22.4	53	3.1	1.11	0.61–2.01	0.739
Treatment class in first trimester ($n=1697$)							
NRTI only	148	8.7	8	5.4	2.08	0.92–4.72	0.080
NNRTI	898	52.9	24	2.7	1.00		
Protease inhibitors	553	32.6	17	3.1	1.16	0.61–2.17	0.654
NNRTI and protease inhibitors	98	5.8	3	3.1	1.15	0.34–3.89	0.822

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.
[a]82.5% (998/1210) of white women were born in the UK or Ireland.
[b]97.6% (6012/6162) of black African women were born in sub-Saharan Africa.
[c]Other risk includes heterosexual, 'from area of high HIV prevalence' and vertical transmission.

more likely than those with information to be preterm or of low birth weight (25 vs. 15%) or to have mothers who were untreated in pregnancy (30 vs. 7%) ($P<0.001$), but not more likely to have early ART exposure (15 vs. 22%, $P=0.478$).

Abnormality rates were lower in infants born to black African mothers than in those born to white mothers, and higher among infants whose mothers were symptomatic (Table 1). Infants with abnormalities were more likely to be delivered prematurely and to be of low birth weight, and girls had a lower reported rate than boys.

There was no significant difference in the unadjusted abnormality rate by ART exposure: 2.8% in unexposed infants, 2.7% in those with late exposure, and 3.1% in those with early exposure ($P=0.690$) (Table 1). After adjusting for potential confounders (maternal ethnicity, age at delivery, injecting drug use and clinical status) neither late [adjusted odds ratio [AOR] = 0.96, 95% CI 0.54–1.71, $P=0.889$] nor early ART exposure (AOR = 1.01, 95% CI 0.54–1.88, $P=0.972$) was significantly associated with congenital abnormality compared with no ART ($n=7179$). AORs were similar to the unadjusted odds ratios presented in Table 1, including for maternal ethnic group and clinical status.

Class of ART was reported for 99.4% (1697/1708) of infants exposed in the first trimester and was not significantly associated with congenital abnormality ($P=0.363$) (Table 1). After adjusting for maternal ethnicity, age, injecting drug use and clinical status,

infants exposed to protease inhibitors showed no significant difference in congenital abnormality rates compared with those exposed to NNRTIs (AOR = 1.09, 95% CI 0.58–2.07, $P = 0.789$), nor did those exposed to NRTIs only (AOR = 1.94, 95% CI 0.84–4.50, $P = 0.123$), or NNRTI- and protease inhibitor-containing regimens (AOR = 1.15, 95% CI 0.34–3.92, $P = 0.823$) ($n = 1679$). Infants exposed only to NRTIs were more likely than those exposed to other drug classes to be reported in earlier years and therefore to be born to young, white, drug-using women [2].

A total of 220 infants were exposed to efavirenz, 205 (93.2%) in early pregnancy; of those exposed early, 2.4% (5/205) had abnormalities reported [undescended testes ($n = 2$), hip dislocation ($n = 2$), hypertrophic pyloric stenosis]. This did not differ significantly from the rate in infants with first trimester exposure to drugs other than efavirenz (3.2%, 48/1503, $P = 0.672$). There were 284 exposures to didanosine, 174 (61.3%) in the first trimester; of those infants with early exposure, 3.4% (6/174) had abnormalities reported [Down's syndrome, heart defect ($n = 2$), hydronephrosis, jejunal atresia, foot abnormality]; this did not differ significantly from the rate for other first trimester ART exposures (3.1%, 47/1534, $P = 0.816$). There were no abnormalities reported in infants only exposed to efavirenz ($n = 15$) or didanosine ($n = 110$) later in pregnancy.

The most commonly reported abnormality types were musculoskeletal (40/232), limb (32/232), heart/circulatory (30/232), and genital organs (22/232; 12 hypospadias, nine undescended testes, one ambiguous genitalia) (Table 2). No category of abnormality was significantly associated with timing of ART (Table 2). Of the 12 cases of hypospadias, all were in infants exposed to zidovudine-containing regimens (0.18%, 12/6711, vs. 0%, 0/792, exposed to zidovudine-sparing regimens, $P = 0.262$). Timing of ART was reported for 11 of these infants: two had early exposure (2/1708, 0.12%; or 2/856 boys, 0.23%) and nine late (9/5427, 0.17%; or 9/2693 boys, 0.33%), with no statistically significant difference between the two groups ($P = 1.00$).

Terminated pregnancies (not included in overall analysis)

Twenty-one congenital abnormalities were reported in 549 terminated pregnancies (1990–2007): anencephaly ($n = 4$), Down's syndrome ($n = 5$), other chromosomal anomaly ($n = 3$), exomphalos, enlarged cerebral ventricles, cleft lip/palate, hydronephrosis, bowel abnormality, heart defect, spina bifida, achondroplasia, and renal agenesis. These 21 terminations were carried out between 12 and 30 weeks gestation, and only five were in women who were on treatment (HAART) in early pregnancy. The overall abnormality rate including these 21 terminations was 3.1% (253/8263, 95% CI 2.7–3.5).

Discussion

An overall congenital abnormality rate of 2.8% (2.1% excluding minor defects) was observed in this unselected population of around 8200 infants. This is consistent with national population estimates of 2–3% for major abnormalities in England and 2.2% for Europe as a whole

Table 2. Reported category of congenital abnormality by timing of antiretroviral therapy exposure.

					Timing of antiretroviral therapy exposure						
	Total		Total with timing information[a]		None		Late (second/third trimester)		Early (first trimester)		
Type of abnormality	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	P^b
Nervous system	17	0.21	16	0.21	1	0.20	11	0.20	4	0.23	0.767
Ear, face, neck and eye	5	0.06	4	0.05	0	0.00	3	0.06	1	0.06	1.000
Heart and circulatory	30	0.36	25	0.33	0	0.00	16	0.29	9	0.53	0.144
Respiratory system	4	0.05	3	0.04	1	0.20	2	0.04	0	0.00	1.000
Cleft palate/lip	7	0.08	7	0.09	1	0.20	5	0.09	1	0.06	1.000
Digestive system	18	0.22	18	0.24	1	0.20	11	0.20	6	0.35	0.262
Genital organs	22	0.27	19	0.25	3	0.60	11	0.20	5	0.29	0.594
Urinary system	20	0.24	19	0.25	1	0.20	11	0.20	7	0.41	0.163
Musculoskeletal	40	0.49	38	0.50	2	0.40	27	0.50	9	0.53	0.846
Limbs	32	0.39	30	0.39	3	0.60	23	0.42	4	0.23	0.279
Integument	11	0.13	10	0.13	0	0.00	7	0.13	3	0.18	0.474
Chromosomal	21	0.25	20	0.26	1	0.20	16	0.29	3	0.18	0.594
Other and unspecified anomalies	2	0.02	2	0.03	0	0.00	1	0.02	1	0.06	0.397
Type not specified	3	0.04	3	0.04	0	0.00	3	0.06	0	0.00	1.000
Total congenital abnormalities	232	2.81	214	2.80	14	2.81	147	2.71	53	3.10	
Total infants	8242		7633		498		5427		1708		

[a]Excludes 18 infants with abnormalities for whom information on timing of treatment was not available.
[b]Fisher's exact test for comparison of first trimester exposure with late or no exposure.

(calculated from EUROCAT data tables, 1980–2006) [11,12].

In common with a number of other large-scale observational studies [3–5], we did not detect any significant association between the rate of reported congenital abnormalities and type or timing of ART in pregnancy; nor did we detect any significant increase in the overall abnormality rate following early exposure to efavirenz ($n = 205$) or didanosine ($n = 174$). The number of reported cases of hypospadias was small ($n = 12$), and rates were similar following early or late ART exposure. The overall excess of abnormalities in boys was mainly accounted for by genital abnormalities, all of which were in boys. The increased abnormality rates in infants born to symptomatic and white women were reported previously [9], but reasons remain unclear.

Although these results are reassuring, the overall rate is likely to be a minimum estimate. In particular, abnormalities not apparent at birth might have been under-reported, either because the birth was only notified through the obstetric scheme, or because diagnosis occurred after the last report. However, reporting of most major abnormalities apparent in the first few weeks of life is likely to be relatively complete. Although ascertainment of early terminations in HIV-infected women is incomplete [2], terminations carried out after a congenital anomaly scan are likely to be well reported.

Infants missing information on congenital abnormality were more likely to be premature, a factor associated with congenital abnormalities; however, they were no more likely to have early ART exposure than those with information provided. Finally, although information on maternal ethnicity, age, injecting drug use and clinical status was available, data on other potential confounders such as maternal smoking and diet during pregnancy, concurrent infections, and non-HIV medication were not.

Although this analysis included over 8200 infants (1700 with early ART exposure), at least 350 exposures to any specific drug would be required to detect a two-fold increase in overall risk with 80% power, and even larger numbers would be required to detect an association with a particular type of abnormality. Nevertheless, these results provide further reassurance that exposure to ART *in utero* does not pose a major risk of fetal anomaly.

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Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990–2006

CL Townsend, M Cortina-Borja, CS Peckham, PA Tookey

MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, London, UK
Correspondence: Ms CL Townsend, MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK. Email c.townsend@ich.ucl.ac.uk

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Objective To describe the changing demographic profile of diagnosed HIV-infected pregnant women over time and trends in pregnancy outcome, uptake of interventions and mother-to-child transmission.

Design National surveillance study.

Setting UK and Ireland.

Population Diagnosed HIV-infected pregnant women, 1990–2006.

Methods Active surveillance of obstetric and paediatric HIV conducted through the National Study of HIV in Pregnancy and Childhood.

Main outcome measures Maternal characteristics, pregnancy outcome, use of antiretroviral therapy, mode of delivery and mother-to-child transmission.

Results A total of 8327 pregnancies were reported, increasing from 82 in 1990 to 1394 in 2006, with an increasing proportion from areas outside London. Injecting drug use as the reported risk factor for maternal HIV acquisition declined from 49.2% (185/376) in 1990–1993 to 3.1% (125/4009) in 2004–2006 ($P < 0.001$), while the proportion of women born in sub-Saharan Africa increased from 43.5% (93/214) in 1990–1993 to 78.6% (3076/3912) in 2004–2006 ($P < 0.004$). Reported pregnancy terminations decreased from 29.6% (111/376) in 1990–1993 to 3.4% (135/4009) in 2004–2006 ($P < 0.001$). Most (56.4%, 3717/6593) deliveries were by elective caesarean section, with rates highest in 1999 (66.4%, 144/217). Vaginal deliveries increased from 16.6% (36/217) in 1999 to 28.3% (321/1136) in 2006 ($P < 0.001$). Use of antiretroviral therapy in pregnancy increased over time, reaching 98.4% (1092/1110) in 2006, and the overall mother-to-child transmission rate declined from 18.5% (35/189) in 1990–1993 to 1.0% (29/2832) in 2004–2006.

Conclusions The annual number of reported pregnancies increased dramatically between 1990 and 2006, with changing demographic and geographic profiles and substantial changes in pregnancy management and outcome.

Keywords Antiretroviral therapy, HIV, pregnancy outcome, surveillance.

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Introduction

Following the introduction of routine antenatal HIV testing throughout the UK and Ireland from 1999 onwards,[1,2] the proportion of HIV-infected pregnant women diagnosed before delivery rose from around 60% in 1999 to over 90% since 2003.[3,4] As a result of high uptake of interventions to reduce the risk of mother-to-child transmission (antiretroviral therapy, elective caesarean section delivery and avoidance of breastfeeding), transmission rates in many parts of Europe have declined to less than 2% in recent years.[5–7] Meanwhile, the prevalence of HIV has continued to rise and more than doubled among women giving birth in England and Scotland from 0.09% to 0.23% between 2000 and 2006, following a more gradual increase during the 1990s.[3,4]

HIV infection in pregnant women and children in the UK and Ireland has been monitored continuously since the late 1980s through unique, population-based, active surveillance schemes, allowing the effects of changes in policy and practice to be observed on a national scale. Reports are sought for all pregnancies diagnosed up to the time of delivery, regardless of timing of booking for antenatal care or uptake of interventions. In this analysis, we explore the changing demographic profile of HIV-infected pregnant women over the course of the HIV

epidemic, along with trends in pregnancy outcome, uptake of interventions and mother-to-child transmission rates.

Methods

Surveillance of obstetric and paediatric HIV in the UK and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC). Pregnancies in women with diagnosed HIV infection are notified through an active obstetric surveillance scheme, run under the auspices of the Royal College of Obstetricians and Gynaecologists. In a parallel reporting scheme, children with HIV infection and infants born to infected women are notified through the British Paediatric Surveillance Unit[8] or directly to the NSHPC. Analyses were based on pregnancies between 1990 and 2006, in women diagnosed with HIV infection before delivery and reported to the NSHPC by June 2007.

Data collected included maternal demographic characteristics and clinical status, pregnancy outcome and delivery details, antiretroviral therapy and child's infection status. Year of delivery was used for births and year of expected date of delivery for other outcomes. For some analyses, years were grouped into five time periods according to availability of interventions: 1990–1993 (pre-antiretroviral therapy), 1994–1996 (zidovudine monotherapy[9]), 1997–1999 (highly active antiretroviral therapy [HAART] and elective caesarean section[10]), 2000–2003 and 2004–2006 (HAART and routine antenatal screening[1]).

Exposure to antenatal antiretroviral therapy was categorised as untreated, monotherapy, dual therapy or HAART (three or more antiretroviral drugs) with or without a protease inhibitor (PI). Information on indication for treatment (whether antiretroviral therapy was prescribed only for prevention of mother-to-child transmission or also because the woman required it for her own health) was requested from 2006. Gestational age was measured in completed weeks. Miscarriage was defined as foetal death up to 23 weeks gestation and stillbirth as foetal death at ≥24 weeks gestation. Delivery at <37 weeks was defined as premature and at <32 weeks as very premature. Low birthweight was defined as <2500 g and very low birthweight as <1500 g. Maternal clinical status was classified as symptomatic if AIDS or HIV-related symptoms were reported during pregnancy.[11] Maternal CD4 cell count and HIV plasma viral load were only routinely reported from 1998 onwards. CD4 count closest to delivery and viral load closest to delivery and up to 7 days postpartum were used in the analyses. Viral loads reported as '<400 copies/ml' ($n = 78$) were reclassified as 200 copies/ml. Mode of delivery was classified as vaginal, elective caesarean section or emergency caesarean section, which included those carried out after rupture of membranes and/or onset of labour, as well as for other obstetric indications (e.g. pre-eclampsia and foetal distress). Detailed maternal information (timing of initiation of antiretroviral therapy, maternal clinical status, viral load and CD4 counts) was collected through the obstetric scheme and was therefore not available for births reported only through the paediatric scheme (~11%).

For the purpose of these analyses, infants were classified as 'uninfected' if a negative polymerase chain reaction (PCR) test was reported after 1 month of age or a negative HIV antibody test after 18 months of age in non-breastfed infants, and 'infected' if a positive PCR was reported at any time or a positive antibody test after 18 months of age.

Reporting rates by geographical area were obtained by dividing the annual number of pregnancies in HIV-infected women reported in each country and English strategic health authority by the number of resident women aged 15–49 years, derived from 2000 census data for the UK[12] and 2002 census data for Ireland.[13] Maps were drawn using R, version 2.4.1.[14]

Data were managed in an Access 2002 database (Microsoft Corp., Redmond, WA, USA) and analysed using Stata 9.0 (Stata Corp., College Station, TX, USA). Means were compared using *t* tests and medians using Wilcoxon tests. Trends in medians were assessed using Cuzick's nonparametric test for trend across ordered groups (function 'nptrend' in Stata).[15] Logistic regression models were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CIs). *P* values for trends were obtained using ordinary logistic regression models; those in Table 1 were adjusted for multiple comparisons using a Bonferroni correction.

Results

All pregnancies

There were 8327 pregnancies in 6788 HIV-infected women; 5540 women had one pregnancy reported during the study period, 1010 two, and 238 three or more. The annual number of reported pregnancies increased 17-fold, from 82 in 1990 to 1394 in 2006, the steepest rise occurring between 1999 and 2003 (Figure 1). There were 116 multiple births; in one twin pair, one infant was stillborn, and there were two twin stillbirths (five stillborn infants altogether). Pregnancy outcomes are shown in Table 1. The 423 pregnancies with other or unknown outcome included two maternal deaths (one suicide and one death from HIV encephalopathy, both in the mid-1990s) and 23 ectopic pregnancies (all ending before 13 weeks gestation); 110 women were known to have left the British Isles before delivery and another 109 were otherwise lost to follow up; information on pregnancy outcome was still pending for 179 pregnancies due to end in 2004–2006.

Maternal characteristics

There were marked changes over time in the demographic profile of the women (Table 1). The proportion of women reported to have probably acquired HIV through injecting drug use or from a drug-using partner declined 10-fold, from

Table 1. Maternal characteristics and pregnancy outcome by time period for 8327 pregnancies

	1990–1993, *n* (%)	1994–1996, *n* (%)	1997–1999, *n* (%)	2000–2003, *n* (%)	2004–2006, *n* (%)	Total, *n*	*P* value (trend)
Pregnancy outcome (*n* = 8327)							
Live birth	235 (62.5)	260 (80.0)	456 (79.2)	2623 (86.3)	3405 (84.9)	6979	
Stillbirth	1 (0.3)	2 (0.6)	7 (1.2)	24 (0.8)	43 (1.1)	77	>0.50
Miscarriage	15 (4.0)	5 (1.5)	32 (5.6)	119 (3.9)	158 (3.9)	329	>0.50
Termination of pregnancy	111 (29.5)	48 (14.8)	70 (12.2)	155 (5.1)	135 (3.4)	519	<0.005
Other/outcome not known*	14 (3.7)	10 (3.1)	11 (1.9)	120 (3.9)	268 (6.7)	423	<0.005
Exposure category (*n* = 8327)							
Other**	191 (50.8)	231 (71.1)	485 (84.2)	2873 (94.5)	3884 (96.9)	7664	
Injecting drug use associated***	185 (49.2)	94 (28.9)	91 (15.8)	168 (5.5)	125 (3.1)	663	<0.001
Region of birth (*n* = 8009)							
UK/Ireland	105 (49.1)	101 (32.8)	143 (25.0)	450 (15.0)	496 (12.7)	1295	<0.004
Europe (excluding UK/Ireland)	9 (4.2)	13 (4.2)	21 (3.7)	69 (2.3)	121 (3.1)	233	>0.50
Sub-Saharan Africa	93 (43.5)	179 (58.1)	381 (66.6)	2309 (76.9)	3076 (78.6)	6038	<0.004
Elsewhere	7 (3.3)	15 (4.9)	27 (4.7)	175 (5.8)	219 (5.6)	443	0.016
Ethnic origin (*n* = 8157)							
White	167 (57.6)	127 (39.3)	150 (26.1)	427 (14.1)	492 (12.5)	1363	<0.003
Black African	115 (39.7)	183 (56.7)	388 (67.5)	2357 (78.0)	3140 (79.5)	6183	<0.003
Other****	8 (2.8)	13 (4.0)	37 (6.4)	236 (7.8)	317 (8.0)	611	<0.003
Age at delivery (*n* = 8244)							
14–24 years	107 (29.9)	63 (19.9)	101 (17.7)	557 (18.5)	704 (17.7)	1532	<0.003
25–34 years	235 (65.6)	234 (73.8)	379 (66.4)	1940 (64.3)	2463 (61.9)	5251	<0.003
35–46 years	16 (4.5)	20 (6.3)	91 (15.9)	519 (17.2)	815 (20.5)	1461	<0.003
Clinical status (*n* = 7253)							
No HIV-related symptoms	258 (78.2)	210 (74.7)	428 (80.6)	2413 (89.0)	3026 (89.0)	6335	
HIV-related symptoms/AIDS	72 (21.8)	71 (25.3)	103 (19.4)	299 (11.0)	373 (11.0)	918	<0.001
Region of pregnancy report (*n* = 8321***)**							
London	191 (50.8)	210 (65.0)	437 (76.0)	1728 (56.9)	1803 (45.0)	4369	
England outside London	65 (17.3)	51 (15.8)	72 (12.5)	823 (27.1)	1711 (42.7)	2722	
Scotland, Wales, Northern Ireland	91 (24.2)	49 (15.2)	30 (5.2)	90 (3.0)	166 (4.1)	426	
Ireland	29 (7.7)	13 (4.0)	36 (6.3)	397 (13.1)	329 (8.2)	804	
Total (*n* = 8327)	376	325	576	3041	4009	8327	

P values are for trends over time, comparing each category against all others combined. *P* values were obtained using logistic regression and adjusted for multiple comparisons using a Bonferroni correction.

*Includes 179 pregnancies due to end in 2004–2006 for which outcome was still pending as of June 2007.

**Includes women with missing exposure information.

***Includes women whose partner acquired HIV through injecting drug use (*n* = 195).

****Other ethnicities include black Caribbean, black other, Asian and mixed.

*****Six infants born in the Channel Islands.

around half in 1990–1993 to less than 5% in 2004–2006 (Table 1). Meanwhile, the proportion of women born in sub-Saharan Africa increased from under half in 1990–1993 to almost 80% in 2004–2006, with a corresponding change in maternal ethnic origin (Table 1). The proportion of women born in Asia rose from 0% (0/214) in 1990–1993 to 2.2% (87/3912) in 2004–2006 (trend: $P = 0.003$). As a proportion of all women with either country of birth or ethnicity reported, those born in the Caribbean or of black Caribbean ethnicity increased from 1.4% (4/293) in 1990–1993 to 3.7% (147/3989) in 2004–2006 (trend: $P = 0.051$). Among women born abroad, information on date of arrival in the British Isles was only available for 55.6% (3735/6714); among these, median time between arrival and delivery was 3.3 years (interquartile range [IQR]: 1.4–6.1 years). Seven women (four born in the British Isles), aged between 15 and 20 years at delivery, were known to have acquired infection vertically from their own mothers.

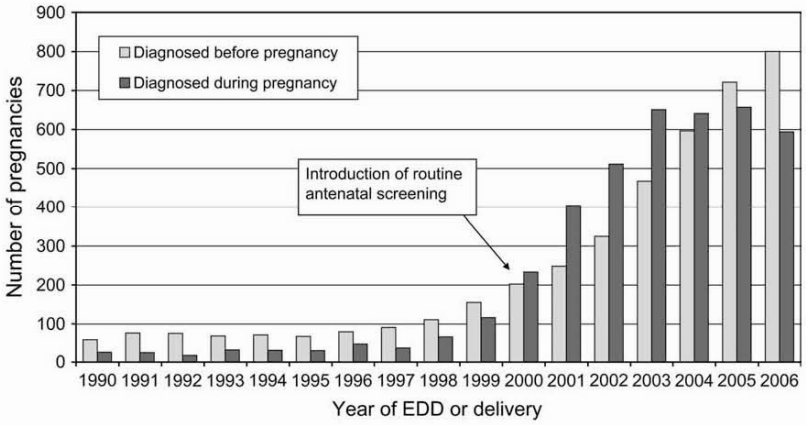

Figure 1. Number of pregnancy reports by timing of maternal diagnosis (before or during pregnancy) and year, 1990–2006. EDD, expected date of delivery. Note: Prevalence of HIV in women giving birth in England and Scotland increased from 0.09% in 2000 to 0.23% in 2006.[4]

Median maternal age at delivery increased over time, from 27.2 years (IQR: 24.4–30.1 years) in 1990–1993 to 30.2 years (IQR: 26.4–34.0 years) in 2004–2006 (trend, $P < 0.001$). There was no evidence of an increase in the proportion of teenage pregnancies (age 14–19 years) over time: 2.8% (10/358) of pregnancies were in teenagers in 1990–1993, 3.9% (22/571) in 1997–1999 and 3.4% (134/3982) in 2004–2006 (trend: $P = 0.276$).

Up to 1999, the majority of pregnancies were in women who already knew their HIV status before they became pregnant (67.0%, 856/1277) (Figure 1). As routine antenatal screening was introduced throughout the British Isles, the proportion of women diagnosed during pregnancy rose to 60.1% (1566/2606) between 2001 and 2003 and then declined subsequently (Figure 1). Among women who knew their HIV status at conception (and with information on where their diagnosis was made), the proportion diagnosed in a previous pregnancy doubled from 18.0% (24/133) in 2000 to 36.1% (181/502) in 2006 (trend: $P < 0.001$). Overall, only 2.9% (120/4112) of antenatal diagnoses were made in the last 2 weeks of pregnancy.

The prevalence of AIDS or HIV-related symptoms in pregnancy decreased over time, from over 20% in the early 1990s to 11% since 2000 ($P < 0.001$) (Table 1).

Geographic origin of reports

There were also changes in the geographic origin of reports. The proportion of pregnancies reported from London increased significantly from about 50% in 1990–1993 to 76% in 1997–1999 (trend: $P < 0.001$) (Table 1). Subsequently, although the number of reports from London continued to rise until 2004, when they stabilised, the proportion reported from elsewhere in England increased significantly from 12.5% in 1997–1999 to 42.7% in 2004–2006 (trend: $P < 0.001$) (Table 1). Figure 2 shows annual reporting rates (number of reports per million women aged 15–49 years) across the UK and Ireland over time. By 2004–2006, rates in most areas of the UK were similar to those in London in 1990–1999. In Ireland, reporting rates stabilised following a substantial rise in the number of reports from only 13 in 1999 to almost 150 in 2003.

Terminations

The proportion of reported pregnancies ending in termination decreased 10-fold from around 30% in 1990–1993 to 3% in 2004–2006 (Table 1). Termination was 2.6 times more common in women diagnosed with HIV before pregnancy than in those diagnosed antenatally (OR = 2.65, 95% CI: 2.18–3.23, $P < 0.001$), but similar declines occurred in both groups (34.7% in 1990–1993 to 4.1% in 2004–2006 for diagnosis before pregnancy, trend: $P < 0.001$; 20.2% to 2.7% for diagnosis during pregnancy, trend: $P < 0.001$). There was no association between HIV exposure category or maternal age and termination, after adjusting for year and timing of diagnosis ($P > 0.50$ in both cases). Median gestational age at termination was 10 weeks (IQR: 9–13 weeks) for women diagnosed before pregnancy and 15 weeks (IQR: 12–19 weeks) for those diagnosed during pregnancy ($P < 0.001$). About 30% (101/335) of previously diagnosed women having terminations were taking antiretroviral therapy at conception. Three terminations were carried out after 24 weeks: one at 25 weeks for major congenital heart defects, one at 30 weeks for anencephaly and one at 29 weeks because of concerns about the woman's mental health.

Miscarriages

Four percent (329/8327) of reported pregnancies resulted in a miscarriage; 80.9% (266/329) occurred before 20 weeks gestation, 10.3% (34/329) at 20–21 weeks and 8.8% (29/329) at 22–23 weeks. The overall miscarriage rate remained constant over time (trend: $P = 0.951$), as did the rate of late miscarriages (≥20 weeks) (trend: $P = 0.890$).

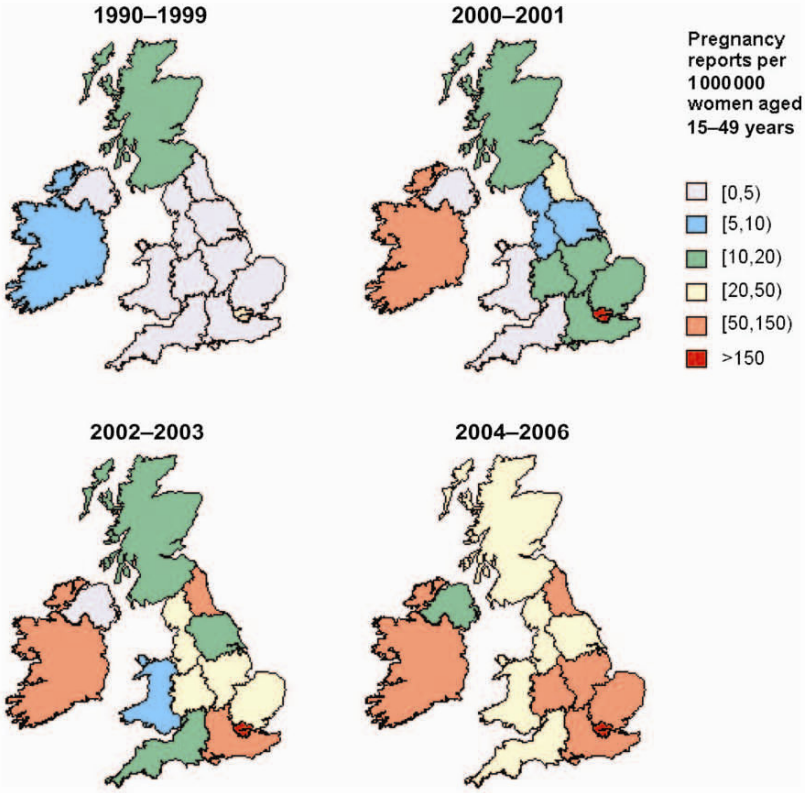

Figure 2. Pregnancy reporting rates in the UK and Ireland by time period and country/region.

Live births and stillbirths

The following results refer to the 85% of pregnancies (7056/8327) resulting in a live birth or stillbirth.

Antiretroviral therapy

Changes in the use of antiretroviral therapy over time are shown in Figure 3. Following the introduction of zidovudine for the prevention of mother-to-child transmission in 1994,[9] uptake of antiretroviral therapy (mostly monotherapy) increased rapidly. Although monotherapy has continued to be offered in some circumstances, it was overtaken by HAART in the late 1990s; by 2006, 98.4% (1092/1110) of diagnosed pregnant women received antiretroviral therapy at some time in pregnancy, 94.5% (1032/1092) of whom received HAART and 4.4% (48/1092) monotherapy.

Type of HAART regimens changed over time, with an increase in the use of PIs among HAART-treated women from 36.1% (43/119) in 1999 to 73.2% (755/1032) in 2006 ($P < 0.001$) (Figure 3). Concerns about toxicity of nevirapine (a non-nucleoside reverse transcriptase inhibitor) in women with high CD4 counts[16] may have led to women with less advanced disease being prescribed PI-containing regimens. Evidence supporting this includes higher median CD4 counts in women on PIs in 2006 than those on other HAART regimens (420 cells/mm^3 versus 330 cells/mm^3, $P < 0.001$); women on PIs were also more likely to have been diagnosed during pregnancy (48.1%, 363/755, versus 28.9%, 80/277, $P < 0.001$) than before.

Among pregnancies in previously diagnosed women, timing of initiation of antiretroviral therapy (before or during pregnancy) was available for 87.3% (2942/3369); once combination therapy became widely available, the proportion on treatment at conception rose rapidly and then stabilised at around 45% (1188/2544) between 1999 and 2006 (trend: $P = 0.936$). In 2006, 39.9% (125/313) of previously diagnosed women on HAART were reported not to require treatment for their own health and only to be taking it for prevention of mother-to-child transmission; in contrast, among those diagnosed during pregnancy and taking HAART, 69.2% (155/224) were doing so only to prevent mother-to-child transmission.

CD4 counts and viral load

CD4 count in pregnancy was reported for 75.9% (4901/6459) of births between 1998 and 2006. Median CD4 count increased significantly, from 315 cells/mm^3 (IQR: 225–425 cells/mm^3) in 1998 to 395 cells/mm^3 (IQR: 270–570 cells/mm^3) in 2006 (trend, $P < 0.001$). Viral load was reported

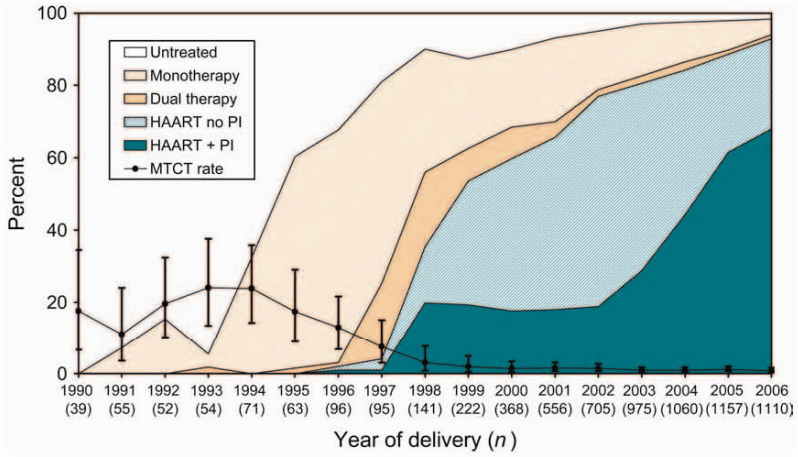

Figure 3. Use of antiretroviral therapy and mother-to-child transmission rates (with 95% CI) by year of delivery, 1990–2006. HAART, highly active antiretroviral therapy; MTCT, mother-to-child transmission; PI, protease inhibitor.

for 78.8% (5092/6459) of births between 1998 and 2006: the proportion with viral load <50 copies/ml increased from 29.0% (27/93) in 1998 to 69.0% (609/882) in 2006 (trend: $P < 0.001$), while median viral load in the remainder decreased from 4494 copies/ml (IQR: 1423–13 400 copies/ml) to 425 copies/ml (IQR: 131–5507 copies/ml) in 2006 (trend: $P < 0.001$).

Mode of delivery

Between 1995 and 2006, most deliveries were by elective caesarean section (56.4%, 3717/6593), increasing from 38.3% (36/94) in 1997 to a high of 66.4% (144/217) in 1999 (trend: $P < 0.001$) (Figure 4). Subsequently, the proportion of elective caesarean sections declined to around 50% (555/1136) in 2006, as vaginal deliveries increased from 16.6% (36/217) to 28.3% (321/1136) between 1999 and 2006 (trend: $P < 0.001$), mostly due to a rise in planned vaginal deliveries (Figure 4). The proportion of emergency caesarean sections increased from 17.1% (37/217) in 1999 to 22.9% (260/1136) in 2006 (trend: $P = 0.001$); among these, the proportion occurring at 37 weeks gestation or later increased from 48.6% (18/37) in 1999 to 60.6% (155/256) in 2006 (trend: $P = 0.021$).

Gestational age, birthweight, stillbirth and neonatal death

Median gestational age was 38 weeks (IQR: 38–39 weeks); 14.2% (975/6874) of deliveries were premature (<37 weeks) and 3.6% very premature (<32 weeks). Median birthweight was 3050 g (IQR: 2720–3370 g); 14.1% (827/5865) of infants were of low birthweight (<2500 g) and 3.1% (179/5865) of very low birthweight (<1500 g). There were no significant

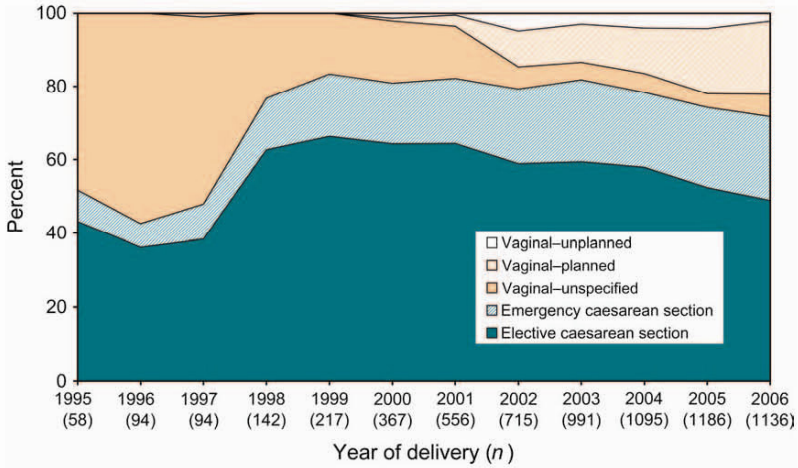

Figure 4. Mode of delivery by year, 1995–2006.

trends over time in the proportion of infants who were premature ($P = 0.564$), very premature ($P = 0.182$), of low birthweight ($P = 0.197$) or of very low birthweight ($P = 0.340$). There were 77 stillbirths (1.1%) and 30 neonatal deaths (0.4% of live births); no trends over time were detected ($P = 0.304$ and $P = 0.460$, respectively).

Mother-to-child transmission

Infection status was reported for 86.9% (6063/6979) of live births (twins were counted as one birth, and none were discordant). The overall mother-to-child transmission rate declined significantly from 18.5% (35/189, 95% CI: 13.3–24.8%) in 1990–1993 to 1.0% (29/2832, 95% CI: 0.7–1.5) in 2004–2006 (Figure 3).

Discussion

The annual number of reported pregnancies in HIV-infected women increased substantially between 1990 and 2006, the sharpest rise occurring between 1999 and 2003, when universal screening strategies were adopted throughout the UK and Ireland[2,17] and during which time HIV prevalence rose in women giving birth.[4] Reductions in mother-to-child transmission rates[5,7] and in overall HIV-associated mortality and morbidity following the introduction of HAART[18] have contributed to an increase in birth rates in HIV-infected women.[19,20] In this population, we observed an increasing number of pregnancies in previously diagnosed women and overall decline in pregnancy terminations. The lower termination rate in women diagnosed during pregnancy, compared with those diagnosed previously, could be due to differential reporting of terminations between the two groups but could also reflect a lack of opportunity for termination among women diagnosed later in pregnancy, as suggested by the later median gestational age at termination in this group. We did not detect an increase in the rate of miscarriage over time. Miscarriages occurring before the first antenatal appointment and terminations carried out in specialist clinics are likely to be underreported because the obstetric surveillance system is focused on women attending for antenatal care; nevertheless, these data provide an indication of trends over time.

In the early 1990s, the epidemic in pregnant women was driven mainly by injecting drug use, while in later years most women originated from areas with generalised HIV epidemics, particularly sub-Saharan Africa. This pattern has also been observed for the UK HIV epidemic more widely.[4] Pregnancies in young women who acquired HIV vertically from their own mothers were reported; this group is likely to increase in the future as girls infected perinatally in the early years of the HIV epidemic reach child-bearing age.[21] Furthermore, an increasing proportion of infected children are now likely to survive into adulthood as a result of advances in the management of paediatric HIV.[22]

There were also changes in the geographic origin of reports within the British Isles. Although reporting rates were highest in London, the proportion of reports from elsewhere increased markedly. This reflects both differences in overall prevalence (e.g. in 2006, an estimated 0.42% of women giving birth in London were HIV infected, compared with 0.14% in the rest of England[4]) and also differences in antenatal detection rates over time. Routine antenatal testing was introduced earlier in London than elsewhere, and uptake was initially higher.[17] Information on asylum status is not collected in this study, but the dispersal of asylum seekers from the South East of England[23] could also have contributed to the increase in reports from outside London.[4,24] Concerns about the impact of this dispersal policy on continuity of HIV care have been voiced.[25,26] These findings highlight the need for a wide range of HIV specialist services throughout the UK and Ireland, particularly in areas where HIV-infected pregnant women were not previously seen and specialist care may not be readily available.

Although the use of antenatal zidovudine monotherapy declined substantially following the introduction of combination therapy, it is still used for some women who do not require HAART for their own health, in accordance with the British HIV Association guidelines.[27] In recent years, most women received HAART in pregnancy, and in 2006, about half were reported to require it for their own health. Among previously diagnosed women, about 45% were already on therapy when they became pregnant.

Women diagnosed in pregnancy and those with higher CD4 counts were more likely to be on PIs than those diagnosed before pregnancy and with lower CD4 counts, suggesting that concerns about nevirapine hepatotoxicity in women with CD4 counts >350 cells/mm^3 contributed to the rise in PI-based HAART from 2003 onwards.[16] The trend towards higher CD4 counts and lower viral loads is likely to reflect not only the beneficial effect of antiretroviral therapy, but also earlier diagnosis of HIV infection resulting from antenatal screening.

As we have previously reported,[28] prematurity rates in women on HAART in this population are about 1.5 times (adjusted OR = 1.51, 95% CI: 1.19–1.93) higher than in those on monotherapy or dual therapy. However, this has not led to an overall significant increase in prematurity rates among diagnosed women over time, probably because of the changing demography and better health of the diagnosed population.

The increase in vaginal deliveries in recent years occurred in the context of guidelines suggesting that women on HAART who achieve viral suppression can opt for a vaginal delivery.[27] This recommendation may also have contributed to the increase in emergency caesarean sections, resulting from unexpected complications arising during planned vaginal deliveries. The increase in the proportion of emergency

procedures being carried out at term supports this interpretation. Although planned caesarean section deliveries usually take place when HIV specialist midwives and obstetricians are on duty, spontaneous vaginal deliveries and emergency caesarean sections may occur unexpectedly, with staff less prepared for dealing with HIV-associated deliveries. While the importance of providing HIV-infected women with a range of treatment and delivery options should not be underestimated, the impact of such policies should be monitored closely, both locally and nationally. Nonetheless, overall mother-to-child transmission rates have remained consistently below 2% since 1999, a remarkable achievement given the diverse and unselected nature of this population. A detailed analysis of factors associated with transmission of infection in the HAART era is reported separately.[29]

This national surveillance study, which relies on the cooperation of a large number of health professionals, is an active reporting system with high response rates (>90%).[30] Comparison of the number of pregnancies reported to the NSHPC with national unlinked anonymous seroprevalence data suggests that case ascertainment for pregnancies ending in a live birth is extremely high.[4]

This report describes the changing epidemiology of HIV in pregnancy in the UK and Ireland and highlights the success of routine antenatal HIV screening policies, both through increased detection of HIV in pregnancy and high uptake of antiretroviral therapy, leading to very low mother-to-child transmission rates. Ongoing established surveillance makes it possible to assess the impact of changes in guidelines and clinical practice on the uptake and effectiveness of interventions and provides timely evidence to help optimise obstetric and perinatal management and outcomes in this diverse population.

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Contribution to authorship

C.L.T. and P.A.T. participated in the data collection and drafted the paper. C.L.T. carried out the statistical analyses with support from M.C.-B. All authors participated in developing the concept of the paper and interpreting the results. All authors commented on all drafts of the paper and approved the final version. P.A.T. is responsible for the NSHPC and is the guarantor.

Ethics approval

Ethics approval for the NSHPC was renewed following review by the London Multi-Centre Research Ethics Committee in 2004 (ref. MREC/04/2/009).

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Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006

Claire L. Townsend[a], Mario Cortina-Borja[a], Catherine S. Peckham[a], Annemiek de Ruiter[b], Hermione Lyall[c] and Pat A. Tookey[a]

Aim: In the United Kingdom (UK) and Ireland, avoidance of breastfeeding and alternative combinations of antiretroviral therapy regimen and mode of delivery are recommended according to maternal clinical status. The aim of this analysis was to explore the impact of different strategies to prevent mother-to-child transmission at a population level.

Design: Comprehensive national surveillance study.

Methods: Pregnancies in diagnosed HIV-infected women in the UK and Ireland are notified to the National Study of HIV in Pregnancy and Childhood; infant infection status is subsequently reported. Factors associated with transmission in this observational study were explored for singleton births between 2000 and 2006.

Results: The overall mother-to-child transmission rate was 1.2% (61/5151, 95% confidence interval: 0.9–1.5%), and 0.8% (40/4864) for women who received at least 14 days of antiretroviral therapy. Transmission rates following combinations recommended in British guidelines were 0.7% (17/2286) for highly active antiretroviral therapy with planned Caesarean section, 0.7% (4/559) for highly active antiretroviral therapy with planned vaginal delivery, and 0% (0/464) for zidovudine monotherapy with planned Caesarean section ($P=0.150$). Longer duration of highly active antiretroviral therapy was associated with reduced transmission after adjusting for viral load, mode of delivery and sex (adjusted odds ratio = 0.90 per week of highly active antiretroviral therapy, $P=0.007$). Among 2117 infants born to women on highly active antiretroviral therapy with viral load less than 50 copies/ml, only three (0.1%) were infected, two with evidence of in-utero transmission.

Conclusion: Sustained low HIV transmission rates following different combinations of interventions in this large unselected population are encouraging. Current options for treatment and delivery offered to pregnant women according to British guidelines appear to be effective.

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Keywords: antiretroviral agents, highly active antiretroviral therapy, HIV, pregnancy, vertical disease transmission, viral load

Introduction

Mother-to-child transmission (MTCT) rates for diagnosed HIV-infected women in the UK and Ireland fell from about 20 to 2% between 1993 and 1998 [1]; transmission rates of 1–2% have been reported in studies from resource-rich countries in recent years, owing to effective antiretroviral therapy (ART), appropriate management of delivery, and avoidance of breastfeeding [2–5].

From the [a]MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, London, the [b]Guys & St Thomas' NHS Foundation Trust, London, and the [c]Imperial College Healthcare NHS Trust, London, UK.

Correspondence to Claire L. Townsend, MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK.

E-mail: c.townsend@ich.ucl.ac.uk

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Highly active antiretroviral therapy (HAART) is now the standard of care in most resource-rich countries. British HIV Association (BHIVA) guidelines also support zidovudine monotherapy and planned Caesarean section as an alternative to HAART for women with high CD4 cell counts and pretreatment viral load of less than 6000–10 000 copies/ml [6]. The benefits of elective Caesarean section in relation to MTCT were demonstrated in the mid-1990s, before HAART was widely used [7], but it is unclear whether planned Caesarean section delivery confers additional benefit for women who achieve viral suppression on HAART [8,9]. Few studies have addressed the impact of different combinations of interventions on MTCT at a population level.

Uptake of antenatal HIV testing rose rapidly following the introduction of routine screening policies in 1999 in Ireland [10] and between 2000 and 2003 in the UK [11], with the estimated proportion of infected women diagnosed before delivery increasing from about 70% in 2000 to about 95% since 2005 [12]. In the UK and Ireland, information on paediatric and obstetric HIV is collected through comprehensive, population-based surveillance. We explore MTCT rates, and factors associated with MTCT, for infants born to diagnosed HIV-infected women between 2000 and 2006.

Methods

Surveillance of obstetric and paediatric HIV in the UK and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC). Pregnancies in women with diagnosed HIV are notified through an active obstetric surveillance scheme, run under the auspices of the Royal College of Obstetricians and Gynaecologists. Children with HIV infection and infants born to infected women are notified through the British Paediatric Surveillance Unit [13], or directly to the NSHPC. This paper is based on singleton births between 2000 and 2006 (when routine antenatal HIV screening and HAART were widely available [12]) to women diagnosed with HIV infection before delivery and reported to the NSHPC by June 2007. Some women ($n = 689$) had two or more pregnancies during the study period. Multiple births were excluded ($n = 98$); none of the twins or triplets was infected (0/165).

Infection status of nonbreastfed infants was classified as 'presumed uninfected' if a PCR test result was negative after 1 month of age, and 'confirmed uninfected' following a subsequent negative PCR after 3 months of age, or a negative HIV antibody test after 18 months of age. Infants were classified as 'presumed infected' if one positive PCR was reported, and 'confirmed infected' if two positive PCR tests were reported, or a positive antibody test after 18 months of age. In these analyses, because preliminary results rarely conflict with later ones, 'presumed' and 'confirmed' results were grouped.

Maternal ART in pregnancy was categorized as none, monotherapy, dual therapy and HAART (three or more drugs); only antepartum treatment was considered in these analyses. HAART was categorized according to whether a protease inhibitor or nonnucleoside reverse transcriptase inhibitor (NNRTI) was included. Gestational age was in completed weeks, and for some analyses categorized as 32 or less, 32–34, 35–36 and at least 37 weeks gestation. Mode of delivery was classified as elective Caesarean section, emergency Caesarean section, and vaginal delivery (reported by obstetric respondents as planned or unplanned). Emergency Caesarean section included those carried out after rupture of membranes or onset of labour, or for other obstetric indications. Duration of rupture of membranes was not requested until 2007 and was not available for this analysis.

Maternal clinical status was classified as symptomatic if AIDS or HIV-related symptoms were reported in pregnancy [14]. Latest antepartum maternal CD4 cell count was used and categorized accordingly: less than 200, 200–349, 350–499 and at least 500 cells/μl. Maternal HIV plasma viral load closest to delivery and up to 7 days postpartum was used (pretreatment viral loads were not available). For some analyses, viral load was classified as less than 50 (undetectable), 50–999, 1000–9999 and at least 10 000 copies/ml; when viral load was used as a continuous variable, midpoints were taken for values below assay detection limits (68 viral loads were reported as 'less than 400 copies/ml'). For logistic regression analyses, viral load was $\log_{10}$ transformed.

Data were managed in an Access 2002 database (Microsoft Corp., Redmond, Washington, USA), compiled using R version 4.1.2 [15], and analysed using Stata version 9.0 (Stata Corp., College Station, Texas, USA). Categorical variables were compared using χ^2 tests or Fisher's exact tests, means using t-tests, and medians using Kruskal–Wallis tests. Logistic regression models were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Likelihood ratio tests were used to compare nested logistic regression models.

Results

Maternal characteristics

There were 5930 singleton infants born between 2000 and 2006, increasing from 358 in 2000 to 1120 in 2006. Most mothers were black African, received antenatal HAART and delivered by elective Caesarean section (Table 1). About 45% (2691/5861) of women were diagnosed before pregnancy. Five women acquired HIV vertically from their own mothers. Among women on

Table 1. Characteristics of mother–child pairs ($n=5930$).

		n	%
Mothers			
Ethnic origin ($n=5875$)	White	775	13.2
	Black African	4630	78.8
	Other	470	8.0
Region of birth ($n=5831$)	British Isles	825	14.1
	Sub-Saharan Africa	4531	77.7
	Elsewhere	475	8.2
HIV exposure group ($n=5930$)	Injecting drug use[a]	241	4.1
	Other[b]	5689	95.9
Clinical status ($n=5134$)	Asymptomatic	4606	89.7
	AIDS or HIV-related symptoms	528	10.3
HIV viral load ($n=4692$)	Undetectable (<50 copies/ml)	2648	56.4
	50–999 copies/ml	1150	24.5
	1000–9999 copies/ml	509	10.9
	At least 10 000 copies/ml	385	8.2
CD4 cell count ($n=4539$)	At least 500 cells/μl	1595	35.1
	350–499 cells/μl	1158	25.5
	200–349 cells/μl	1241	27.3
	Less than 200 cells/μl	545	12.0
Antiretroviral therapy ($n=5760$)	None[c]	186	3.2
	Monotherapy	712	12.4
	Dual therapy	136	2.4
	HAART	4726	82.1
Mode of delivery ($n=5901$)	Elective Caesarean section	3368	57.1
	Emergency Caesarean section	1223	20.7
	Vaginal delivery	1310	22.2
	Planned	745	12.6
	Unplanned	176	3.0
	Unspecified	389	6.6
	Median (interquartile range)		
Age at delivery ($n=5882$)	29.8 years (26.2–33.6 years)		
Infants			
Sex ($n=5903$)	Male	2978	50.4
	Female	2925	49.6
Gestational age ($n=5760$)	At least 37 weeks	5029	87.3
	35–36 weeks	360	6.2
	32–34 weeks	218	3.8
	Less than 32 weeks	153	2.7
	Median (interquartile range)		
Birth weight ($n=5050$)	3.1 kg (2.7–3.4 kg)		

HAART, highly active antiretroviral therapy.
[a]Includes women who acquired HIV from a drug using partner.
[b]Includes women with missing exposure information.
[c]Includes women known to have declined treatment ($n=50$), been diagnosed late (i.e. within 2 weeks of delivery, $n=43$) or delivered prematurely (<32 weeks, $n=12$; 33–37 weeks, $n=6$).

HAART, 24.1% (1075/4469) started it before pregnancy, and the median gestational age at initiation for those starting in pregnancy was 25.9 weeks [interquartile range (IQR): 22.4–28.9 weeks]. Median gestational age at initiation of monotherapy was 28.0 weeks (IQR: 25.4–30.0). Median viral load was less than 50 copies/ml (IQR: less than 50–184 copies/ml) following HAART and 355 copies/ml (IQR: 54–1977 copies/ml) following monotherapy.

Infants with unreported infection status

Infection status was not yet reported for 13.1% (779/5930) of infants at time of analysis [but for only 8.7% (419/4810) of infants born 2000–2005]. Reasons for unreported infection status were: paediatric notification not yet received (birth only reported through obstetric scheme; 54.0%, 421/779), paediatric follow-up pending (28.4%, 221/779), child lost to follow up (11.4%, 89/779), child left the UK/Ireland (3.5%, 27/779), and death (mostly associated with prematurity or congenital abnormality) (2.7%, 21/779).

Children with unreported infection status did not differ significantly from those with known infection status in terms of maternal HIV exposure group, clinical status or mode of delivery, but more were born at less than 32 weeks gestation (5.0%, 38/758, versus 2.3%, 115/5002, $P<0.001$), to untreated women (5.9%, 43/733, versus 2.8%, 143/5027, $P<0.001$), and to women with viral load of at least 1000 copies/ml (21.8%, 130/596, versus 18.7%, 764/4096, $P=0.061$), factors associated with each other.

Overall mother-to-child transmission rates

The overall transmission rate was 1.2% (61/5151, 95% CI: 0.9–1.5%), and lower in 2003–2006 (1.0%, 38/3695) than in 2000–2002 (1.6%, 23/1456) ($P=0.069$). Transmission from women on ART for at least the last 14 days of pregnancy was 0.8% (40/4864, 95% CI: 0.6–1.1%), regardless of type of therapy or mode of delivery. Transmission was not associated with maternal ethnic group, birth region, or HIV exposure group (data not shown), or maternal symptoms or low CD4 cell count (Table 2). Univariable risk factors for transmission included no maternal ART, vaginal delivery (particularly if unplanned), prematurity (less than 32 weeks gestation), female sex and detectable viral load (Table 2). Table 3 shows all infants (and proportion infected) by maternal ART and mode of delivery.

In the multivariable analysis ($n=4892$; Table 4) including ART, mode of delivery, gestational age and sex (but not viral load), being untreated (adjusted odd ratio (AOR) = 9.08, $P<0.001$) was the strongest risk factor for transmission, and girls were more likely to be infected than boys (AOR = 1.91, $P=0.023$). Prematurity (less than 32 weeks) was a significant risk factor for transmission (AOR = 3.55, $P=0.010$); however, of the seven women who had infected infants born at less than 32 weeks gestation, all were either untreated ($n=3$) or treated for less than 3 weeks (range: 1–19 days), and all but one delivered vaginally. Prematurity was not a significant risk factor for transmission among women on HAART (AOR = 1.32, 95% CI: 0.30–5.82, $P=0.714$).

In the multivariable model, vaginal delivery was associated with a nonsignificant 1.8-fold increased risk of transmission compared with elective Caesarean section (AOR = 1.82, $P=0.076$). Information on whether vaginal deliveries were planned or unplanned was available for 69.1% (775/1122). After adjusting for ART, gestational age and sex, unplanned vaginal delivery was associated with a significantly increased risk of transmission (AOR = 4.16, 95% CI: 1.66–10.41, $P=0.002$) compared with elective Caesarean section, but planned vaginal delivery was not (AOR = 1.56, 95% CI: 0.65–3.72, $P=0.319$).

The association between mode of delivery and transmission varied by type of therapy, but owing to small numbers could not be explored adequately using

Table 2. Mother-to-child transmission rates by risk factors ($n=5151$ mother–child pairs with infection status reported).

	Total	*n* infected	MTCT rate (%)	Crude OR	95% CI
Antiretroviral therapy ($n=5027$)					
HAART	4120	40	1.0	1.00	
Dual therapy	126	1	0.8	0.82	0.11–5.98
Monotherapy	638	3	0.5	0.48	0.15–1.56
None	143	13	9.1	10.20	5.33–19.53
Mode of delivery ($n=5131$)					
Elective Caesarean section	2953	23	0.8	1.00	
Emergency Caesarean section	1056	17	1.6	2.08	1.11–3.92
Vaginal delivery	1122	21	1.9	2.43	1.34–4.41
Planned	618	7	1.1	1.46	0.62–3.42
Unplanned	157	9	5.7	7.75	3.52–17.04
Unspecified	347	5	1.4	1.86	0.70–4.93
Maternal clinical status ($n=4456$)					
Asymptomatic	3994	45	1.1	1.00	
AIDS or HIV-related symptoms	462	7	1.5	1.35	0.61–3.01
HIV viral load ($n=4096$)					
Undetectable (<50 copies/ml)	2309	3	0.1	1.00	
50–999 copies/ml	1023	12	1.2	9.12	2.57–32.4
1000–9999 copies/ml	429	6	1.4	10.9	2.70–43.8
At least 10 000 copies/ml	335	20	6.0	48.8	14.4–165.2
Missing	1035	20	1.9		
CD4 cell count ($n=3962$)					
At least 500 cells/μl	1389	11	0.8	1.00	
350–499 cells/μl	1011	11	1.1	1.38	0.60–3.19
200–349 cells/μl	1080	11	1.0	1.29	0.56–2.98
Less than 200 cells/μl	482	7	1.5	1.85	0.71–4.79
Missing	1168	21	1.8		
Gestational age ($n=5002$)					
At least 37 weeks	4383	45	1.0	1.00	
35–36 weeks	315	3	1.0	0.93	0.29–3.00
32–34 weeks	189	4	2.1	2.08	0.74–5.86
Less than 32 weeks	115	7	6.1	6.25	2.75–14.17
Sex of infant ($n=5141$)					
Male	2580	22	0.9	1.00	
Female	2561	39	1.5	1.80	1.06–3.04

CI, confidence interval; HAART, highly active antiretroviral therapy; MTCT, mother-to-child transmission; OR, odds ratio.

Table 3. Number of infants and proportion infected by maternal antiretroviral therapy and mode of delivery ($n = 5131$[a]).

	Caesarean section						Vaginal delivery									All deliveries		
	Elective			Emergency			Planned			Unplanned			Unspecified					
		Infected			Infected			Infected			Infected			Infected			Infected	
ART	Total	*n*	%	Total	*n*	%	Total	*n*	%	Total	*n*	%	Total	*n*	%	Total	*n*	%
HAART	2286	17	0.7	877	15	1.7	559	4	0.7	122	4	3.3	263	0	0.0	4107	40	1.0
Dual therapy	69	1	1.4	18	0	0.0	13	0	0.0	2	0	0.0	23	0	0.0	125	1	0.8
Monotherapy	464	0	0.0	108	0	0.0	37	1	2.7	9	1	11.1	19	1	5.3	637	3	0.5
Untreated	52	3	5.8	34	2	5.9	8	2	25.0	24	4	16.7	25	2	8.0	143	13	9.1
Missing	82	2	2.4	19	0	0.0	1	0	0.0	0	0	–	17	2	11.8	119	4	3.4
Total	2953	23	0.8	1056	17	1.6	618	7	1.1	157	9	5.7	347	5	1.4	5131	61	1.2

ART, antiretroviral therapy; HAART, highly active ART.
[a]Twenty infants with missing information on mode of delivery are excluded from this table, as none was infected.

interaction terms; analyses stratified by therapy are presented later.

Viral load was reported for 79.5% (4096/5151) of women, but for significantly fewer untreated than treated women (49.7%, 71/143, versus 82.3%, 4021/4884, $P < 0.001$), and infected than uninfected infants (67.2%, 41/61, versus 79.7%, 4055/5090, $P = 0.024$). The closest viral load to delivery was a median 23 days before delivery (IQR: 10–44 days). In the multivariable analysis ($n = 4084$) controlling for ART, mode of delivery, gestational age and sex, each $\log_{10}$ increase in viral load was associated with a 2.4-fold increased risk of transmission (AOR = 2.41, $P < 0.001$) (Table 4). In this model, lack of ART (AOR = 3.17, $P = 0.023$) and vaginal delivery (AOR = 2.40, $P = 0.033$) were strongly associated with transmission, but gestational age and sex were not.

Although HIV-infected women in the UK and Ireland are recommended to formula feed, breastfeeding was reported in 0.6% (29/4399) of infants with information provided; three were infected, all born to untreated women (two declined ART, one was diagnosed close to delivery).

Transmission following highly active antiretroviral therapy

MTCT rate for women on HAART was 1.0% (40/4120) (Table 2) and was not significantly different when HAART included an NNRTI (0.9%, 18/1959), a protease inhibitor (1.1%, 20/1795, $P = 0.625$), both an

Table 4. Adjusted odds ratios for mother-to-child transmission.

		Model 1: all cases ($n = 4892$), not adjusting for viral load				Model 2: cases with viral load reported ($n = 4084$), not adjusting for viral load			Model 3: cases with viral load reported ($n = 4084$), adjusting for viral load		
	n (model 1)	AOR	95% CI	*P*-value	*n* (models 2 and 3)	AOR	95% CI	*P*-value	AOR	95% CI	*P*-value
Antiretroviral therapy											
HAART	4012	1.00			3399	1.00			1.00		
Dual therapy	120	0.86	0.12–6.33	0.883	75	1.60	0.21–11.98	0.647	1.71	0.22–13.03	0.606
Monotherapy	629	0.56	0.17–1.82	0.334	539	0.72	0.22–2.38	0.587	0.57	0.17–1.91	0.366
None	131	9.08	4.54–18.16	<0.001	71	8.58	3.34–22.03	<0.001	3.17	1.17–8.59	0.023
Mode of delivery											
Elective Caesarean section	2797	1.00			2399	1.00			1.00		
Emergency Caesarean section	1023	1.67	0.80–3.48	0.172	847	1.48	0.62–3.57	0.380	1.89	0.79–4.52	0.153
Vaginal delivery	1072	1.82	0.94–3.53	0.076	838	1.82	0.84–3.93	0.128	2.40	1.08–5.35	0.033
Gestational age											
At least 37 weeks	4288	1.00			3584	1.00			1.00		
35–36 weeks	306	0.84	0.25–2.81	0.773	255	0.82	0.19–3.60	0.788	0.49	0.11–2.23	0.359
32–34 weeks	185	1.63	0.54–4.94	0.390	153	1.73	0.47–6.34	0.405	1.17	0.32–4.29	0.816
Less than 32 weeks	113	3.55	1.36–9.30	0.010	92	4.38	1.48–12.99	0.008	2.35	0.77–7.20	0.134
Sex of infant											
Male	2447	1.00			2053	1.00			1.00		
Female	2445	1.91	1.09–3.33	0.023	2031	1.52	0.80–2.87	0.198	1.58	0.82–3.04	0.170
HIV viral load											
Per $\log_{10}$ increase					4084				2.41	1.91–3.05	<0.001

AOR, adjusted odds ratio; CI, confidence interval; HAART, highly active antiretroviral therapy.

NNRTI and a protease inhibitor (0.8%, 2/258), or neither (0%, 0/108, $P=0.847$). Comparing protease inhibitor with NNRTI regimens, there was no difference in MTCT rates after adjusting for mode of delivery, sex and viral load (AOR = 1.31, 95% CI: 0.62–2.76, $P=0.482$) (as previously noted, gestational age was not a significant risk factor for transmission in women on HAART and was therefore excluded from these analyses). HAART at conception was associated with a lower risk of transmission than HAART started in pregnancy (0.1%, 1/928, versus 1.3%, 39/2967, $P=0.001$), but this was only of borderline significance after adjusting for mode of delivery, sex and viral load (AOR = 0.18, 95% CI: 0.02–1.33, $P=0.093$). Among women who started HAART during pregnancy, those who transmitted ($n=34$) started later than those who did not (median gestational age at initiation: 30.1 weeks, IQR: 27.4–32.6 weeks, versus 25.9 weeks, IQR: 22.4–28.7 weeks, $P<0.001$). Each additional week of treatment corresponded to a 10% (AOR = 0.90, 95% CI: 0.84–0.97, $P=0.007$) reduction in the risk of transmission after adjusting for viral load (closest to delivery), mode of delivery and sex.

Among women on HAART, there was no statistically significant difference in MTCT rates between elective Caesarean section (0.7%, 17/2286) and planned vaginal delivery (0.7%, 4/559; AOR = 1.24, 95% CI: 0.34–4.52, $P=0.746$, adjusted for sex and viral load); viral load was undetectable in 58.7% (1135/1934) of those having elective Caesarean sections, and 79.0% (417/528) having planned vaginal deliveries ($P<0.001$). Only three transmissions were reported among 2117 infants born to women on HAART with undetectable viral load (0.1%, 95% CI: 0.0–0.4%); two were born by elective Caesarean section (0.2%, 2/1135) and one by planned vaginal delivery (0.2%, 1/417). Two of the three infants (one born vaginally) had positive PCR results within 72 h of birth, suggesting possible in-utero transmission. MTCT rates were higher in women on HAART who had emergency Caesarean sections (1.7%, 15/877) or unplanned vaginal deliveries (3.3%, 4/122) compared with elective Caesarean sections ($P=0.027$ and $P=0.019$, respectively).

Eighteen other women had infected infants despite HAART and either planned vaginal delivery or elective Caesarean section. For 10 of them, one or more of the following applied: short duration of treatment, high viral load near delivery (range: 8500–285 000), adherence problems. There were six transmissions from women with low but detectable viral load (≥50 and <1000 copies/ml); two had planned vaginal deliveries (2.5%, 2/81) and four elective Caesarean sections (0.8%, 4/471, $P=0.215$). Two of these six infected infants had positive PCR results within 72 h of birth (both born by elective Caesarean section). The remaining two women received HAART for at least 1 month, but no viral loads were reported.

Information on neonatal prophylaxis was provided for 20 of the 21 infants infected despite maternal HAART and planned vaginal or elective Caesarean section delivery, and all were treated; 18 had breastfeeding status reported, and none was breastfed.

Transmission following zidovudine monotherapy

The mothers of 638 infants received prophylactic zidovudine monotherapy in pregnancy, and three infants were infected (0.5%, 95% CI: 0.1–1.4%); all three women were treated for less than 1 month, had detectable viral load (range: 474–3000 copies/ml) and delivered vaginally. The transmission rate following monotherapy and elective Caesarean section was 0% (0/464, 95% CI: 0–0.8%), with median viral load of 400 copies/ml (IQR: 61–1992 copies/ml); this transmission rate was not significantly different from that following HAART and planned vaginal delivery (0.7%) or elective Caesarean section (0.7%, $P=0.150$). The transmission rate following monotherapy and emergency Caesarean section was 0% (0/116, 95% CI: 0–3.4%), with median viral load of 597 copies/ml (IQR: 84–3195 copies/ml).

Adjustment for unreported infection status

Potential bias introduced by excluding infants with unreported infection status was investigated by computing likely infection status based on maternal treatment and viral load categories. A crude transmission rate of 9.1% was assumed for all untreated women (Table 2) and those with missing treatment information (viral load was unavailable for over 70% of these women). Among treated women, actual transmission rates by viral load levels were 0.1% (3/2299) for viral load of less than 50 copies/ml, 1.2% (12/1003) for 50–999 copies/ml, 1.4% (6/414) for 1000–9999 copies/ml, 4.6% (14/305) for at least 10 000 copies/ml and 1.0% (9/863) for those where viral load was not recorded. Using these transmission rates to compute likely infection status, an estimated 1.8% (14/779) of children with unreported infection status would be infected, which would increase the overall transmission rate marginally to 1.3% (75/5930, 95% CI: 1.0–1.6%).

Discussion

These results are based on observational data collected in the UK and Ireland. Routine antenatal HIV testing and professional guidelines [6] were available throughout this period, outlining a range of strategies for the management of HIV in pregnancy. Although these guidelines recommend that most women should receive HAART in pregnancy, zidovudine monotherapy with planned Caesarean section remains an alternative for asymptomatic women with high CD4 cell count and low viral load. A more tolerant approach to mode of delivery for women who achieve full viral suppression on HAART

has become evident, with rates of planned vaginal delivery rising [16].

MTCT rates remained very low: 1.2% overall (slightly lower in recent years) and 0.8% for women on treatment for at least the last 2 weeks of pregnancy. These low rates are consistent with reports from elsewhere in Europe and the United States [3,5]. We observed similar transmission rates among women on HAART who had elective Caesarean sections or planned vaginal deliveries (0.7% in both groups), and the transmission rate was particularly low (0.1%) in the 2100 women on HAART who achieved viral suppression. In cases where transmission occurred despite HAART and planned vaginal or elective Caesarean section delivery, most infections could be explained by failure to reduce viral load, mainly because of short duration of treatment or adherence problems, or to in-utero transmission. An audit undertaken to investigate circumstances surrounding cases of perinatal HIV transmission in England reported similar findings [17].

In this population, zidovudine monotherapy is likely to have been used selectively according to the BHIVA guidelines [6], a strategy associated with low rates of drug resistance [18,19]. Our findings suggest that selective zidovudine monotherapy combined with elective Caesarean section is a reasonable approach for preventing MTCT (no infections reported in over 450 infants).

Lack of ART and vaginal delivery, particularly unplanned, remained significantly associated with transmission after controlling for viral load near delivery. Before the widespread use of HAART, prematurity was identified as a risk factor for transmission [20]. In this analysis, the increased risk of transmission associated with very premature delivery was not observed in women on HAART. An increased risk of MTCT for girls has been previously reported, both for HIV and for hepatitis C virus [21–23], but in this study, the increased rate for girls was no longer significant when the analysis was restricted to cases where maternal viral load was recorded, possibly owing to reduced numbers.

Among women on HAART, we found no difference in transmission rates by type of regimen, even though differences in response to protease inhibitor and NNRTI-based regimens in pregnant women have been reported [24]. Any effect, however, might have been attenuated in recent years by the restriction of nevirapine to women with CD4 cell counts below 250 cells/μl [6,25], who may also have higher baseline viral loads.

There was evidence that being on HAART at conception and starting HAART earlier in pregnancy were associated with a lower risk of transmission after adjusting for viral load; this could be due to an increased risk of in-utero transmission before initiation of treatment. In these analyses we used viral loads closest to delivery, which might not reflect the infant's exposure to high maternal viral load at earlier stages of pregnancy. Of the nine infected children born to women with low or undetectable viral load, four had detectable virus at birth and were probably infected during fetal life. With postpartum transmission in developed countries now rare and intra-partum transmission highly preventable, in-utero transmission is likely to account for an increasing proportion of perinatal infections. The benefits of early treatment, however, must be weighed against concerns about drug toxicities and adverse pregnancy outcomes [26–28]; we have previously reported an increased risk of premature delivery associated with HAART in this population [29].

This national surveillance study is designed to include all pregnant women diagnosed with HIV any time up to delivery, regardless of maternal characteristics or uptake of interventions. Alignment of NSHPC reports with unlinked anonymous neonatal seroprevalence data suggests that about 95% of HIV-infected women are diagnosed before delivery [12]. Given the active nature of the complementary obstetric and paediatric reporting systems, and the high estimated overall detection rates, very few cases of diagnosed HIV infection in pregnancy are likely to remain unreported.

Children whose infection status had not yet been reported were more likely than those with known infection status to have recognized risk factors for transmission. We have, however, shown that although this bias could potentially lead to an underestimate of the overall transmission rate any effect is likely to be small. Owing to the observational nature of these data they should be interpreted in the context of current guidelines, in which interventions are recommended on the basis of timing of maternal diagnosis, clinical presentation, response to treatment, personal circumstances and choice. Since a randomized trial would be inappropriate, these population data provide important evidence to support the targeted use of different combinations of interventions for preventing MTCT.

The low rate (1.2%) of MTCT of HIV among diagnosed pregnant women in the UK and Ireland is a remarkable achievement. Continuing to improve the offer and uptake of antenatal HIV testing could have a significant impact on further reducing MTCT, since most perinatally acquired infection is now in infants whose mothers are among the approximately 5% of infected women who remain undiagnosed at delivery [12,17]. Ensuring that women are diagnosed in time to take up appropriate interventions remains a priority, and early testing for all pregnant women should continue to be promoted. Our findings suggest that offering HIV-infected women choices about HIV treatment and mode of delivery, according to current guidelines, has led to very low rates of MTCT.

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C.L.T. and P.A.T. participated in the data collection and drafted the paper. C.L.T. carried out the statistical analyses with support from M.C.-B. All authors participated in developing the concept of the paper and interpreting the results. All authors commented on drafts of the paper and approved the final version. P.A.T. is responsible for the NSHPC and is the guarantor.

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Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland

Claire L. Townsend, Mario Cortina-Borja, Catherine S. Peckham and Pat A. Tookey

Objective: To explore the association between antiretroviral therapy in pregnancy and premature delivery, birthweight, stillbirth and neonatal mortality, in pregnancies in HIV-infected women delivering between 1990 and 2005.

Design: Pregnancies in women with diagnosed HIV infection in the UK and Ireland are notified to the National Study of HIV in Pregnancy and Childhood (NSHPC) through a well-established surveillance scheme.

Results: The prematurity rate (< 37 weeks gestation) was higher in women on highly active antiretroviral therapy (HAART) (14.1%, 476/3384) than in women on mono/dual therapy (10.1%, 107/1061), even after adjusting for ethnicity, maternal age, clinical status and injecting drug use as the source of HIV acquisition [adjusted odds ratio (AOR) = 1.51, 95% confidence interval (CI), 1.19–1.93; $P = 0.001$]. Delivery at < 35 weeks was even more strongly associated with HAART (AOR = 2.34; 95% CI, 1.64–3.37; $P < 0.001$). The effect was the same whether or not HAART included a protease inhibitor. In comparison with exposure to mono/dual therapy, exposure to HAART was associated with lower birthweight standardized for gestational age ($P < 0.001$), and an increased risk of stillbirth (AOR = 2.27; 95% CI, 0.96–5.41; $P = 0.063$).

Conclusions: These findings, based on comprehensive population surveillance, demonstrate an increased risk of prematurity associated with HAART, and a possible association with other perinatal outcomes, including stillbirth and birthweight. Although the beneficial effects of antiretroviral therapy on mother-to-child transmission are indisputable, monitoring antiretroviral therapy in pregnancy remains a priority.

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Keywords: antiretroviral agents, highly active, antiretroviral therapy, premature birth, pregnancy outcome, stillbirth, birth weight

Introduction

Since the widespread implementation of routine antenatal HIV screening in the UK and Ireland from 2000 onwards, the proportion of HIV-infected pregnant women diagnosed before delivery has increased substantially, from less than one-third in the mid-1990s to over 90% since 2003 [1]. Diagnosed women are offered interventions to reduce the risk of mother-to-child transmission (MTCT), including antiretroviral therapy and elective caesarean section delivery, and are advised not to breastfeed [2]. As a result of improving detection rates and high uptake of interventions, transmission rates in the UK and elsewhere in Europe decreased from 15–25% in

From the Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, UK.
Correspondence to Dr Pat A. Tookey, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, 30 Guilford Street, London, WC1N 1EH, UK.
E-mail: p.tookey@ich.ucl.ac.uk

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the early 1990s to less than 2% in recent years [3–5]. Highly active antiretroviral therapy (HAART) is routinely prescribed in pregnancy [2,6], and a substantial proportion of previously diagnosed women are on HAART at conception and throughout pregnancy [2]. Although antiretroviral therapy provides clear benefits, these highly potent drugs could also have adverse effects on the pregnancy or developing fetus.

Prematurity is associated with increased morbidity and mortality [7], and has been identified as a risk factor for MTCT [8]. A possible association between antiretroviral therapy and prematurity was initially identified in 1998 when premature delivery was reported in 10 of 30 women taking combination therapy in a Swiss study [9]. Combined analysis of Swiss and European Collaborative Study (ECS) data confirmed that prematurity rates were higher among women on combination therapy compared with untreated women [10]; the ECS subsequently reported a two-fold increase in prematurity associated with HAART, compared with mono or dual therapy [11]. A potential biological mechanism for this association has also been proposed [12]. In contrast, reports from the United States (US) have been conflicting. Although several studies found no association between prematurity and combination therapy [13–15], Cotter *et al* reported a 1.8-fold increased risk associated with protease inhibitor (PI)-containing therapy [16]. Differences in population characteristics, indication for treatment, data collection or analytical approaches could account for these discrepant findings [17,18].

The association between HAART and other pregnancy outcomes is also unclear; an increased risk of fetal death [19] and very low birthweight (< 1500 g) [13] has been reported in some studies, but not in others [15,16,20]. There is so far no evidence of an association between antiretroviral therapy (ART) and congenital abnormalities [21–23].

In the UK and Ireland, information on all pregnancies in diagnosed HIV-infected women is collected routinely through national surveillance: we explore the use of ART in pregnancy and its relationship with prematurity, birthweight, stillbirth and neonatal mortality in this unselected population.

Methods

The National Study of HIV in Pregnancy and Childhood

Surveillance of obstetric HIV infection in the UK and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC). A confidential, voluntary, active reporting scheme was established in June 1989 under the auspices of the Royal College of Obstetricians and Gynaecologists; a designated respondent for each maternity unit (generally a midwife, obstetrician or genito-urinary physician) reports all pregnancies in HIV-infected women, regardless of outcome, and data are collected on a standard questionnaire. A parallel paediatric HIV reporting scheme has been in operation since 1986 [24]: HIV-infected children and infants born to infected women are reported by paediatricians, mainly through the British Paediatric Surveillance Unit's active monthly reporting scheme.

This paper is based on pregnancies resulting in a singleton live birth or stillbirth delivered between 1990 and 2005, in women diagnosed with HIV before delivery and reported to the NSHPC by March 2006. Analyses were based on pregnancies rather than women, and some women were therefore included more than once.

Definitions

Exposure to antiretroviral therapy in pregnancy was categorized as untreated, monotherapy, dual therapy or HAART (three or more antiretroviral drugs). As dual therapy regimens are uncommon, and of lower potency than HAART [25], they were grouped with monotherapy in these analyses. HAART was categorized according to whether PIs and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs) were included. Timing of therapy was classified as 'early' if antiretroviral therapy was initiated before or during the first trimester of pregnancy ($\leq$ 12 completed weeks gestation).

Year of delivery was grouped into 1990–1993 (pre-antiretroviral therapy era), 1994–1999 (early antiretroviral therapy era [26]) and 2000–2005 (HAART and routine antenatal screening era [6,27]). Mode of delivery was reported as vaginal, or elective or emergency caesarean section. Gestational age was in completed weeks and prematurity was defined as delivery at < 37 weeks gestation. Delivery by elective caesarean section should not impact on prematurity rates, as the British HIV Association (BHIVA) guidelines recommend that it take place at 38 weeks gestation [2]. Stillbirth was defined as fetal death at $\geq$ 24 weeks gestation, and neonatal death as death in the first 28 days of life. *Z*-scores for birthweight standardized for gestational age were obtained using British standards [28].

Maternal clinical status was classified as symptomatic if AIDS or HIV-related symptoms were reported at any time in pregnancy. CD4 cell count (not routinely reported before 2000) was categorised as < 200, 200–499 and $\geq$ 500 cells/μl; latest antepartum CD4 cell count was used in the analyses. HIV RNA viral load (VL) (recorded from 1998 onward) was classified as < 1000 or $\geq$ 1000 copies/ml to allow for changes over time in assay detection limits; the closest VL to delivery was included in analyses, measured at least 1 week after antiretroviral therapy initiation and before 15 days postpartum.

Statistical methods

Data were managed in a Microsoft Access 2002 database (Microsoft Corp., Redmond, Washington, USA) and analysed using Stata 9.0 (Stata Corp., College Station, Texas, USA) [29]. Categorical variables were compared using χ^2 tests or Fisher's exact test, and means using *t*-tests. Logistic regression models were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CI). All adjusted ORs (AORs) were adjusted for the following potential confounders [7]: injecting drug use (IDU) as the probable route of HIV infection, ethnic origin, maternal age at delivery and clinical status; interaction terms between these factors and antiretroviral therapy were also considered. Likelihood ratio tests (LRT) were used to compare nested logistic regression models. To allow for repeat pregnancies in the same woman, generalized linear mixed effects were used to fit logistic regression models accounting for random effects attributed to the mother [30]. Only random effects on the intercept of the linear predictor were considered. All ORs and *P*-values were calculated using this class of models.

Results

Over the study period, 5009 pregnancies were reported and the overall prematurity rate was 13.3% (667/5009). Seventy pregnancies (1.3%) had inadequate information on antiretroviral therapy; these did not differ from those for which treatment information was available in terms of prematurity, but a higher proportion occurred before 2000 (34 versus 17%; $P<0.001$), and were in white women (27 versus 17%; $P=0.023$) and women with IDU-acquired infection (12 versus 5%; $P<0.001$).

There were clear baseline differences between antiretroviral therapy-treated and untreated women, and between women on mono/dual therapy and those on HAART, reflecting changes in the characteristics of HIV-infected women over time and trends in antiretroviral therapy use in pregnancy (Table 1).

Pregnancies in untreated women

There were 494 pregnancies in untreated women; the prematurity rate in this group was 11.0% (20/181) in

Table 1. Maternal characteristics by category of antiretroviral therapy received in pregnancy (n = 4939).

	Untreated (*n* = 494)		Mono/dual therapy (*n* = 1061)		HAART (*n* = 3384)		HAART versus mono/dual therapy	
Maternal characteristic	*n*	%	*n*	%	*n*	%	χ^2	*P*-value
Ethnic origin								
White	164	33.7	211	19.9	439	13.0		
Black African	303	62.3	763	72.0	2647	78.2		
Other	19	3.9	86	8.1	297	8.8	30.6	<0.001
Age at delivery								
14–24 years	124	25.2	239	22.5	572	16.9		
25–34 years	334	67.7	681	64.2	2161	63.9		
35–46 years	35	7.1	140	13.2	651	19.2	31.0	<0.001
HIV exposure group								
From high prevalence area	311	63.0	808	76.2	2849	84.2		
Injecting drug use	99	20.0	68	6.4	81	2.4		
Other/no known risk	84	17.0	185	17.4	454	13.4	54.3	<0.001
Timing of diagnosis								
Before this pregnancy	253	51.2	397	37.4	1606	47.5		
During this pregnancy	241	48.8	664	62.6	1778	52.5	32.9	<0.001
Clinical status								
No HIV-related symptoms	418	86.2	962	91.5	2919	86.9		
HIV-related symptoms/AIDS	67	13.8	89	8.5	440	13.1	16.3	<0.001
CD4 cell count[a]								
≥ 500 cells/μl	63	30.9	387	47.9	895	30.1		
200–499 cells/μl	110	53.9	372	46.0	1628	54.7		
< 200 cells/μl	31	15.2	49	6.1	454	15.3	109.0	<0.001
Viral load[b]								
< 1000 copies/ml	35	31.0	379	70.4	2418	91.6		
≥ 1000 copies/ml	78	69.0	159	29.6	223	8.4	188.4	<0.001
Mode of delivery								
Elective caesarean section	83	29.3	702	68.1	1996	59.4		
Emergency caesarean section	55	19.4	144	14.0	689	20.5		
Vaginal	145	51.3	185	17.9	677	20.1	29.4	<0.001
Year of delivery								
1990–1993	181	36.6	14	1.3	0			
1994–1999	156	31.6	317	29.9	164	4.8		
2000–2005	157	31.8	730	68.8	3220	95.2	575.5	<0.001

[a]CD4 cell count was available for 85.2% (3785/4445) of treated and 41.3% (204/494) of untreated women.
[b]Viral load was available for 71.5% (3179/4445) of treated and 22.9% (113/494) of untreated women.

1990–1993, 16.7% (26/156) in 1994–1999 and 19.7% (31/157) in 2000–2005.

Since the introduction of antiretroviral therapy, women remaining untreated at delivery were likely to have delivered before antiretroviral therapy could be initiated, due to late diagnosis and/or premature delivery; for premature deliveries in 2000–2005, diagnosis was within 14 days of delivery in 29% (9/31) of untreated but only 2% (9/522) of treated women ($P < 0.001$). Due to biases introduced by these changes over time, it was not appropriate to use these pregnancies as a comparison group.

Pregnancies in antiretroviral therapy-treated women

Most of the 4445 pregnancies with antiretroviral therapy exposure were in black African women, and few were in women with IDU-acquired infection (Table 1). Median maternal age at delivery was 29.7 years [range, 14.8–47.4; interquartile range (IQR), 26.2–33.6]. Most deliveries were by elective caesarean section (Table 1), and median gestational age was 38 weeks (IQR, 38–39). Compared with HAART, mono/dual therapy was associated with being younger, white, acquiring HIV through IDU, VL $\geq$ 1000 copies/ml and CD4 cell count $\geq$ 500 cells/μl (Table 1).

Most women took HAART in pregnancy (Table 2), and HAART more frequently included an NNRTI than a PI. Over a quarter of women on HAART were on treatment early in pregnancy (Table 2), whereas most women taking mono/dual therapy started later (94.9%, 1007/1061). Actual date of initiation of antiretroviral therapy was available for 89.3% (3968/4445) of pregnancies: the proportion in which antiretroviral therapy was initiated late (within 2 weeks of delivery) did not differ by type of antiretroviral therapy, even among women who delivered prematurely (data not shown).

Table 2. Categories of antiretroviral therapy.

Antiretroviral therapy	*n*	%
Type of antiretroviral therapy ($n = 4445$)		
Monotherapy	904	20.3
Dual therapy	157	3.5
HAART	3384	76.1
Type of HAART ($n = 3384$)		
With NRTIs only	69	2.0
With NNRTI, no PI	1831	54.1
With PI, no NNRTI	1256	37.1
With PI and NNRTI	228	6.7
Timing of HAART initiation ($n = 3299$)		
Before pregnancy/in first trimester	914	27.7
Between 13 and 26 weeks gestation	1287	39.0
After 26 weeks gestation	1098	33.3

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Prematurity

The overall prematurity rate in antiretroviral therapy-treated pregnancies was 13.1% (583/4445; 95% CI, 12.1–14.2); 51.8% (302/583) of premature deliveries were at < 35 weeks, including 23.3% (136/583) at < 32 weeks. Prematurity was not significantly associated with maternal age or ethnic origin (Table 3); significant risk factors were IDU-acquired infection, HIV-related symptoms in pregnancy, and CD4 cell count < 500 cells/μl (Table 3). Viral load was not associated with premature delivery in univariable analysis; 13.9% (53/382) of pregnancies in women with VL $\geq$ 1000 copies/ml delivered prematurely, compared with 11.4% (320/2797) with VL < 1000 copies/ml ($P = 0.168$).

The prematurity rate was 14.1% (476/3384) in pregnancies with HAART exposure and 10.1% (107/1061) with mono/dual therapy exposure (Table 3) (OR = 1.49; 95% CI, 1.18–1.89; $P = 0.001$). The association remained significant after adjusting for clinical status, IDU-acquired infection, ethnic origin and maternal age (AOR = 1.51; 95% CI, 1.19–1.93; $P = 0.001$). There were no significant interactions. Including CD4 cell count in the model reduced the AOR slightly, but the association remained significant (Table 3). The multivariable analyses were also repeated for 3179 pregnancies with recorded VL (excluding CD4 cell count to avoid collinearity and loss of power): both VL $\geq$ 1000 copies/ml (AOR = 1.45; 95% CI, 1.02–2.06; $P = 0.039$) and HAART (AOR = 1.47; 95% CI, 1.03–2.09; $P = 0.032$) were independently associated with prematurity. The prematurity rate in pregnancies with missing CD4 cell count was higher than in those with CD4 count (17 versus 12%, respectively, $P < 0.001$), and similarly for VL (16 versus 13%, $P = 0.015$), probably reflecting lack of opportunity for testing women in premature labour.

Information on other risk factors for prematurity, such as previous obstetric history and prior preterm delivery, was not available. However, parity was reported for 90.9% (4039/4445) of pregnancies: the magnitude of the association between HAART and prematurity was similar for parous and nulliparous women (AOR = 1.46; 95% CI, 1.08–1.98; $P = 0.012$, and AOR = 1.60; 95% CI, 1.06–2.43; $P = 0.026$, respectively).

The association between HAART and prematurity was consistent across time periods (1994–1999, AOR = 1.53; 95% CI, 0.85–2.75; $P = 0.159$; 2000–2005, AOR = 1.50; 95% CI, 1.13–2.00; $P = 0.005$). Excluding 157 pregnancies with dual therapy exposure did not substantially alter the findings (AOR = 1.39; 95% CI, 1.08–1.79; $P = 0.010$), nor did excluding 913 pregnancies with treatment (mostly HAART) in early pregnancy (AOR = 1.45; 95% CI, 1.13–1.87; $P = 0.003$). The association was also present in 1034 pregnancies with diagnosis before pregnancy, but *no* early antiretroviral therapy (AOR = 1.43; 95% CI, 0.93–2.21; $P = 0.105$).

Table 3. Odds ratios for premature delivery (< 37 completed weeks gestation).

			Univariable ($n=4445$)[a]		Multivariable ($n=4407$)[a,b]		Multivariable - subset with CD4 counts ($n=3761$)[a,b,c]	
	n	% premature	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Antiretroviral therapy								
Mono/dual therapy	1061	10.1	1.00		1.00		1.00	
Highly active antiretroviral therapy	3384	14.1	1.49 (1.18–1.89)	0.001	1.51 (1.19–1.93)	0.001	1.39 (1.05–1.83)	0.022
Ethnic origin								
White	650	14.2	1.00		1.00		1.00	
Black African	3410	12.7	0.88 (0.68–1.14)	0.340	1.07 (0.78–1.45)	0.682	0.99 (0.70–1.40)	0.947
Other	383	15.1	1.20 (0.73–1.58)	0.710	1.32 (0.87–2.00)	0.193	1.32 (0.83–2.08)	0.238
Maternal age at delivery								
< 25 years	811	12.8	1.00		1.00		1.00	
25–34	2842	12.9	1.01 (0.79–1.30)	0.940	0.96 (0.75–1.25)	0.775	0.88 (0.66–1.17)	0.384
≥ 35	791	14.0	1.11 (0.82–1.52)	0.476	1.02 (0.75–1.40)	0.880	0.97 (0.69–1.37)	0.870
HIV exposure group								
From high prevalence area, other or no known risk	4296	12.8	1.00		1.00		1.00	
Injecting drug use	149	22.1	2.05 (1.32–3.18)	0.001	2.28 (1.36–3.83)	0.002	1.95 (1.07–3.58)	0.030
Clinical status								
No HIV-related symptoms	3881	12.4	1.00		1.00		1.00	
HIV-related symptoms/AIDS	529	18.5	1.66 (1.28–2.16)	< 0.001	1.59 (1.23–2.08)	0.001	1.54 (1.15–2.06)	0.003
CD4 cell count								
≥ 500 cells/μl	1282	10.1	1.00					
200–500 cells/μl	2000	13.4	1.39 (1.09–1.76)	0.007	–		1.34 (1.05–1.71)	0.018
< 200 cells/μl	503	15.9	1.74 (1.29–2.40)	0.001	–		1.55 (1.11–2.18)	0.010

AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio. Odds ratios adjusted for: [a]repeat pregnancies, [b]injecting drug use as the source of HIV infection, ethnic origin, maternal age and clinical status, [c]CD4 cell count.

In HAART-exposed pregnancies, there was no association between timing of treatment initiation and prematurity: 16.4% (150/914) following early exposure, compared with 14.6% (188/1287) following initiation at 13–26 weeks gestation (AOR = 1.11; 95% CI, 0.85–1.44; $P = 0.460$).

The association between HAART and prematurity was more pronounced for deliveries at < 35 and < 32 weeks than at < 37 weeks gestation (Table 4). Delivery at < 35 weeks occurred in 7.8% (264/3384) of HAART-exposed pregnancies and 3.6% (38/1061) of mono/dual therapy-exposed ($P < 0.001$) pregnancies, and at < 32 weeks in 3.6% (121/3384) and 1.4% (15/1061) respectively ($P = 0.001$).

Among 3384 HAART-exposed pregnancies, premature delivery occurred in 8.7% (6/69) of those with exposure to NRTIs only, 14.3% (261/1831) of those with NNRTI exposure, 13.5% (169/1256) with PI exposure, and 17.5% (40/228) with both PI and NNRTI exposure ($\chi^2 = 4.37$, $P = 0.224$). The risk of premature delivery was not significantly different according to whether HAART included a PI or not (AOR = 0.96; 95% CI, 0.78–1.19; $P = 0.738$).

Birthweight

Mean birthweight was slightly but significantly lower for infants exposed to HAART *in utero* than for infants exposed to mono/dual therapy (2.98 versus 3.10 kg, respectively, $P < 0.001$). After standardizing for

Table 4. Odds ratios for the relative risk of premature delivery for pregnancies in women on highly active antiretroviral therapy compared with mono/dual therapy (baseline).

	Univariable ($n=4445$)[a]		Multivariable ($n=4407$)[a,b]		Multivariable - subset with CD4 cell counts ($n=3761$)[a,b,c]	
Timing of delivery	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
< 37 weeks	1.49 (1.18–1.89)	0.001	1.51 (1.19–1.93)	0.001	1.39 (1.05–1.83)	0.022
< 35 weeks	2.30 (1.62–3.27)	< 0.001	2.34 (1.64–3.37)	< 0.001	2.02 (1.35–3.04)	0.001
< 32 weeks	2.74 (1.51–4.95)	0.001	2.70 (1.48–4.92)	0.001	2.63 (1.30–5.33)	0.007

AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio. Odds ratios adjusted for: [a]repeat pregnancies, [b]injecting drug use as the source of HIV infection, ethnic origin, maternal age and clinical status, [c]CD4 cell count.

gestational age, HAART-exposed infants were significantly lighter than those exposed to mono/dual therapy (mean z-scores for birthweight standardized for gestational age: HAART, −0.06; mono/dual therapy, 0.06, $P=0.002$). Results were similar for premature and non-premature infants, but not statistically significant for the 469 premature infants (mean z-scores: HAART, −0.08; mono/dual therapy, 0.08, $P=0.329$).

Perinatal deaths

The stillbirth rate was 12.7 per 1000 births (43/3384) following HAART exposure, compared with 5.7 per 1000 (6/1061) following mono/dual therapy exposure (OR = 2.26; 95% CI, 0.96–5.34; $P=0.062$; AOR = 2.27; 95% CI, 0.96–5.41; $P=0.063$). The neonatal mortality rate was 4.2 per 1000 live births (14/3341) following HAART, and 1.9 per 1000 (2/1055) following mono/dual therapy (OR = 2.20; 95% CI, 0.50–9.69; $P=0.298$). Twelve of 21 neonates who died were born at < 32 weeks gestation, five with *in utero* exposure to HAART.

Discussion

Through this national surveillance study, information is sought on all diagnosed HIV-infected pregnant women in the UK and Ireland; comparison with unlinked anonymous survey data suggests that over 90% of affected pregnancies were diagnosed and reported between 2003 and 2005 [1], and substantial case ascertainment bias is therefore unlikely. The demographic characteristics of HIV-infected women and antiretroviral therapy use in pregnancy changed over time. In particular, untreated women formed a heterogeneous group: almost 40% were reported before antiretroviral therapy was widely used and about 30% since 2000, when not receiving antiretroviral therapy was generally associated with late diagnosis, a more likely scenario where pregnancy is curtailed by premature delivery. Comparison of prematurity rates between treated and untreated women was therefore not appropriate. Only 70 pregnancies were excluded due to insufficient treatment information, some of which were undoubtedly in untreated women: their prematurity rate was similar to the overall rate, and excluding this group is unlikely to introduce significant bias.

Among pregnancies in treated women, HAART was associated with a 1.5-fold increased risk of premature delivery compared with mono/dual therapy, and the effect was stronger for delivery at < 35 or < 32 weeks gestation. The association was maintained after adjusting for IDU-acquired infection, ethnic origin, maternal age, and factors associated with maternal immunosuppression (HIV-related symptoms, CD4 cell count, VL). Prior preterm delivery has been postulated as a potential confounder in the association between antiretroviral therapy and prematurity [14,18]; although we had no information on prior preterm delivery, our findings were similar for parous and nulliparous women. Information on other potential risk factors for prematurity, such as socio-economic status, smoking, and use of alcohol or illicit drugs, is not collected through the surveillance system. However, despite substantial changes over time in the demographic characteristics of HIV-infected pregnant women, including risk factors for prematurity, the magnitude of the association with HAART was similar in 1994–1999 and 2000–2005.

Findings from other studies exploring the association between antiretroviral therapy and prematurity have been inconsistent, possibly due to differences in populations or study protocols. In contrast to cohort studies and clinical trials, which recruit selectively and require consent, these analyses are based on comprehensive population surveillance. Our results concur with other European studies showing an increased risk of prematurity associated with HAART [10,11]. A US study has also reported a similar association [16], but limited to PI-containing regimens. In our study, substantial numbers of women were on PI- and non-PI-containing regimens, and an increased risk of prematurity was observed in both groups.

An important source of bias in observational studies exploring antiretroviral therapy and premature delivery is indication for treatment [18]. The BHIVA guidelines now suggest monotherapy or HAART for pregnant HIV-infected women who do not require treatment for their own health [2], but only HAART for women who do. Although information on indication for treatment was not available, when we adjusted for HIV-related symptoms and CD4 cell count as a proxy for maternal health, the association between HAART and prematurity remained. We also carried out a sub-analysis of pregnancies in women diagnosed before pregnancy but not already on treatment (and possibly less likely to require treatment for their own health than those on antiretroviral therapy at conception); the magnitude of the association (AOR = 1.43) was similar to that in the main model, although not statistically significant.

To explore the association between duration of treatment and prematurity, we compared pregnancies with early HAART initiation with those with initiation at 13–26 weeks gestation. We excluded pregnancies delivered after 26 weeks because of bias introduced by differences in opportunity to start treatment according to timing of delivery; our failure to detect a statistically significantly increased risk of prematurity with longer duration of treatment could have been due to the reduced sample size. Few studies have explored the effect of duration of HAART exposure [11,16], possibly because timing of initiation of treatment is not always available, and because analysis is complicated since premature delivery naturally shortens the duration of antenatal treatment.

The association between low CD4 cell count and prematurity has been reported elsewhere, as has the link with IDU [10], which we detected despite having information only on IDU-associated HIV acquisition, rather than IDU during pregnancy. Although evidence suggests that black African women in the UK generally have higher prematurity rates than white women [31,32], rates were similar in our study; however, white HIV-infected pregnant women are unlikely to be representative of the general white pregnant population with respect to current or past IDU, or other risk factors for premature delivery. The overall prematurity rate in this study (13.3%) was substantially higher than the 7–8% reported for the general population in the UK [32,33], probably due in part to differences in maternal characteristics. Although there are no national data on trends in gestational age, the rate of low birthweight (< 2500 g) in singleton infants in England and Wales remained relatively constant between 1983 (5.8%) and 2000 (6.1%) [34].

HAART-exposed infants were of lower birthweight (standardized for gestational age) than those exposed to mono/dual therapy, regardless of prematurity, although in clinical terms this difference was small. The association between HAART and birthweight standardized for gestational age has not been reported elsewhere, but birthweight < 1500 g was associated with combination therapy in one US study [13], and an increase in low birthweight over time has been reported in the ECS [11]. Although stillbirth and neonatal mortality rates were higher in HAART-exposed infants, this difference was not statistically significant, possibly due to insufficient numbers.

Our findings, based on routine population surveillance in the UK and Ireland, support the premise that HAART in pregnancy is associated with an increased risk of premature delivery. The beneficial effects of prophylactic ART on MTCT rates are indisputable; observed transmission rates in this population have remained below 2% since 2000. Nevertheless, these findings raise important questions about the type of treatment to be recommended to pregnant women, particularly for those not needing HAART for their own health. The number of births to diagnosed HIV-infected women in the UK and Ireland continues to rise, and an increasing number of women are on HAART at conception. Monitoring adverse pregnancy and perinatal outcomes should remain a priority, and further research into the mechanisms leading to preterm labour in HIV-infected women is needed.

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Antiretroviral Therapy and Congenital Abnormalities in Infants Born to HIV-1–Infected Women in the United Kingdom and Ireland, 1990 to 2003

Claire L. Townsend, MSc, Pat A. Tookey, PhD, Mario Cortina-Borja, PhD, and Catherine S. Peckham, MD

Summary: Antiretroviral therapy (ART) in pregnancy substantially reduces the risk of mother-to-child transmission of HIV, but concerns exist about the potential for teratogenic effects. This analysis was undertaken to explore the relation between ART in pregnancy and birth defects in infants born to HIV-infected women in the United Kingdom and Ireland between 1990 and 2003. Comprehensive obstetric and pediatric HIV surveillance is carried out through the National Study of HIV in Pregnancy and Childhood. Congenital abnormalities were reported in 101 of 3172 infants (100 of 3120 pregnancies). There was no statistically significant association between the prevalence of congenital abnormalities and exposure to ART overall: 3.4% (90 of 2657 pregnancies) in exposed pregnancies and 2.2% (10 of 463 pregnancies) in nonexposed pregnancies ($P = 0.166$); prevalence was similar whether or not exposure occurred in the first trimester: 3.7% (20 of 541 pregnancies) after early exposure and 3.1% (80 of 2579 pregnancies) without early exposure ($P = 0.476$). There was also no significant association with type of ART in early pregnancy (ie, highly active antiretroviral therapy [HAART] vs. mono- or dual therapy, HAART with protease inhibitor and/or nonnucleoside reverse transcriptase inhibitor). The lack of association was maintained after adjustment for potential confounding factors. These findings are reassuring, but continued monitoring is essential in view of the increasing number of women on therapy at conception and the likely continuing diversity of drug regimens.

Key Words: congenital abnormality, antiretroviral therapy, HIV

(*J Acquir Immune Defic Syndr* 2006;42:91 94)

Prophylactic antiretroviral therapy (ART) in pregnancy has had a marked impact on the risk of mother-to-child transmission of HIV-1. Since the mid-1990s, the use of ART in pregnancy has increased dramatically and is currently recommended for all HIV-infected pregnant women in Europe.[1,2] In the British Isles by the end of the 1990s, the mother-to-child transmission rate from diagnosed women to their infants had declined to approximately 2%[3] and is now probably 1% to 2%. Meanwhile, the prevalence of HIV infection among pregnant women is increasing, as are diagnosis rates. Although most infected women currently start treatment in the second half of pregnancy, increasing numbers are on ART for their own health at the time of conception.

Animal studies of individual antiretroviral drugs have revealed little evidence of teratogenicity,[4,5] but data on exposure to combinations of antiretroviral drugs are lacking. Spinal malformations have been found in monkeys exposed to efavirenz in utero, and spinal anomalies in human fetuses exposed to efavirenz have been reported.[6,7] There has also been concern over the use of ART alongside folate antagonists; increased rates of abnormalities have been reported in infants with combined exposure to both types of drugs.[8] To date, however, prospective monitoring through the Antiretroviral Pregnancy Registry (www.APRegistry.com) has not revealed a significant overall increase in the risk of congenital abnormalities among infants exposed to ART in the first trimester compared with those exposed subsequently,[9,10] nor has a significantly increased prevalence of abnormalities been reported in European cohorts.[11–13]

Information on congenital abnormalities in infants born to HIV-infected women in the United Kingdom and Ireland has been collected through the national surveillance system since 1989. A wide variety of combinations and types of ART have been available and recommended to diagnosed pregnant women during that period. Most births to diagnosed women have occurred since 2000, and some of these women were taking highly active antiretroviral therapy (HAART) at conception and in the first trimester of pregnancy in many different combinations. In this report, we explore the relation between ART and birth defects in this comprehensive population-based study.

METHODS

Surveillance of obstetric and pediatric HIV infection in the United Kingdom and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC). The study combines 2 parallel reporting schemes: the obstetric scheme was established in June 1989 under the auspices of the Royal College of Obstetricians and Gynaecologists (RCOG),

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From the Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, United Kingdom.
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The views expressed in the publication are those of the authors and not necessarily those of the Department of Health.

Ethics approval for the National Study of HIV in Pregnancy and Childhood was renewed after review by the London Multi-Centre Research Ethics Committee (MREC ref. MREC/04/2/009) on January 28, 2004.
Reprints: Pat A. Tookey, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, United Kingdom (e-mail: p.tookey@ich.ucl.ac.uk).

and the pediatric scheme was established in 1986 through the British Paediatric Surveillance Unit.[14] Obstetric respondents in every maternity unit in the United Kingdom and Ireland are contacted 4 times a year and report all pregnancies in diagnosed HIV-infected women seen in the previous 3 months. Children with HIV infection as well as infants born to HIV-infected women are reported by pediatricians and followed up to establish outcome. Both reporting systems are active, confidential, and comprehensive and have high response rates. This report is based on all pregnancies resulting in a live birth or stillbirth in women diagnosed before delivery due to deliver between January 1990 and December 2003 and reported to the NSHPC by the end of 2004. Routinely collected information includes maternal demographic details, type and timing of ART, mode of delivery, outcome of pregnancy, and congenital abnormalities identified by the time of notification (usually in the first few weeks of life). Abnormalities were classified according to the World Health Organization (WHO) International Classification of Diseases, 10th revision.[15] Infants with multiple abnormalities were counted only once, but all reported abnormalities are listed in Table 1. Abnormalities defined as "minor" in these analyses were polydactyly; undescended testes; spina bifida occulta; accessory nipple; minor skin, feet, or facial abnormalities; strawberry nevi; and subclinical subependymal cysts.

Exposure to ART was categorized according to the number of antiretroviral drugs taken during pregnancy. Only 4% of women were on dual therapy, and these were combined with those on monotherapy. Any combination of 3 or more drugs was categorized as HAART. To explore the effect of different classes of drugs included in HAART regimens, HAART was further categorized according to whether a protease inhibitor (PI) and/or a nonnucleoside reverse transcriptase inhibitor (NNRTI) was included. Exposure to ART in the first trimester of pregnancy (up to and including 12 completed weeks) was referred to as "early" exposure.

Data were managed in a Microsoft Access 2002 database and analyzed using Stata 8.2 for Windows (Stata Corporation, College Station, TX). Differences in prevalence were assessed using χ^2 tests. The relation between ART exposure and congenital abnormality was assessed using odds ratios (ORs). Likelihood ratio tests were used to compare nested logistic regression models, which were fitted to allow for potential confounding factors.

RESULTS

Overall, 3147 pregnancies ending in a live birth or stillbirth were reported, including 51 twin pairs and 1 set of triplets. Information on type and timing of ART was available for 3120 pregnancies; the remaining 27 were excluded from analyses (no abnormalities were reported in this group). Most pregnancies (2286 [73.3%] of 3120) occurred between 2000 and 2003.

A total of 73.6% (2279 of 3095) of pregnancies were in black women, and 18.7% (578 of 3095) of pregnancies were in white women. The median maternal age at delivery was 29 years (range: 16–44 years). Approximately 10% (302 of 3120) of pregnancies were in women who probably acquired infection through injecting drug use (IDU). Most deliveries were by elective cesarean section (1745 [60.8%] of 2868

TABLE 1. Congenital Abnormalities in 101 Infants With and Without Exposure to ART in the First Trimester of Pregnancy

	No ART Exposure in First Trimester		ART Exposure in First Trimester	
Type of Abnormality	**n**	**List of Abnormalities**	**n**	**List of Abnormalities**
Nervous system	7	Range of abnormalities*	2	Hydrocephalus, subependymal cysts
Heart and circulatory system	6	Septal defect (3), Fallot tetralogy, patent ductus arteriosus, atrioventricular canal defect	4	Septal defect (2), truncus arteriosus‖, Ebstein anomaly‖
Respiratory system	3	Cystic lung, pulmonary hypoplasia‖, unspecified lung abnormality	1	Pulmonary stenosis
Musculoskeletal	15	Range of abnormalities†	7	Range of abnormalities‡
Limbs	13	Polydactyly	0	
Cleft palate and/or lip	4	Lip (1), palate (1), lip and palate (2)	0	
Ear, face, neck, or eye	4	Ear abnormality, ptosis of eye, cataracts, cornea opacification	1	Mouth abnormality
Digestive system	6	Bowel abnormality (3, 1‖, 1§), biliary atresia	1	Jejunal atresia
Skin, hair, nails, or breast	7	Accessory nipple (2), strawberry nevi (4), skin flaps around neck	1	Skin tag
Genital organs	8	Hypospadias (3), undescended testes (5)	1	Hypospadias
Urinary system	6	Hydronephrosis (5), dysplastic kidney	2	Renal dilatation (2)
Chromosomal	6	Down syndrome (5), trisomy 18‖	0	
Other anomalies	1	Beckwith-Wiedman syndrome	1	Prader-Willi syndrome
Not specified	1	§	0	
Total congenital abnormalities	87	(6 infants had 2 defects each)	21	(1 infant had 2 defects)

*Hydrocephalus (1 stillbirth, 1 live birth), absent corpus callosum, spina bifida, microcephaly, holoprosencephaly (neonatal death), and cerebral atrophy.
†Talipes (10), achondroplasia (neonatal death), Caffey syndrome, diaphragmatic hernia, hip dislocation, and vertebral/rib abnormalities.
‡Talipes, hemivertebrae, exomphalos, spina bifida occulta, hip dislocation (2), and foot abnormality.
§Stillbirth.
‖Neonatal death.

deliveries), and the median gestational age was 38 completed weeks (interquartile range: 38–39 weeks).

Of 3120 pregnancies, 14.8% (463 of 3120 pregnancies) were in untreated women, 26.5% (827 of 3120 pregnancies) were in women on mono- or dual therapy, and 58.7% (1830 of 3120 pregnancies) were in women on HAART. HAART included an NNRTI in 67.8% (1240 of 1830) of cases, a PI in 23.8% (436 of 1830) of cases, a PI and an NNRTI in 6.5% (119 of 1830) of cases, and neither in 1.9% (35 of 1830) of cases. Among pregnancies in treated women, 20.4% (541 of 2657 pregnancies) were in women on ART early in pregnancy, with most on HAART (496 [91.7%] of 541 pregnancies).

Congenital abnormalities were reported in 101 of 3172 live- and stillborn infants (100 [3.2%] of 3120 pregnancies, 95% confidence interval [CI]: 2.6% to 3.9%). Excluding 30 minor defects, the congenital abnormality rate was 2.2% (70 of 3120 pregnancies, 95% CI: 1.8% to 2.8%). Seven infants had multiple abnormalities. There were 3 twin pregnancies in which 1 or both twins had an abnormality (4 infants). Abnormalities were reported in 3 of the 32 stillborn infants and in 7 of the 16 neonates who died within 28 days of birth. Among 2603 liveborn infants for whom HIV infection status was established, 102 (3.9%) were infected, including 1 with a major heart abnormality.

There was no significant association between overall exposure to ART during pregnancy and prevalence of congenital abnormalities: prevalence was 3.4% (90 of 2657 pregnancies) after any exposure to ART and 2.2% (10 of 463 pregnancies) with no exposure (OR = 1.6, 95% CI: 0.8 to 3.1; $P = 0.166$). There was also no association with early ART exposure: prevalence of abnormalities was 3.7% (20 of 541 pregnancies) after early exposure and 3.1% (80 of 2579 pregnancies) with no early exposure (OR = 1.2, 95% CI: 0.7 to 2.0; $P = 0.476$). There was no apparent clustering of any particular type of abnormality after early exposure (see Table 1). Excluding the 30 minor abnormalities made no difference to these findings.

The prevalence of abnormalities did not vary according to the type of ART taken early in pregnancy. Among the 541 pregnancies with early exposure, abnormalities were reported in 3.8% (19 of 496 pregnancies) of those exposed to HAART and 2.2% (1 of 45 pregnancies) of those exposed to mono- or dual therapy (OR = 1.8, 95% CI: 0.2 to 13.4; $P = 0.584$). Prevalence of congenital abnormalities was 3.4% (7 of 205 pregnancies) if early HAART included a PI and 4.1% (12 of 291 pregnancies) if it did not (OR = 0.8, 95% CI: 0.3 to 2.1; $P = 0.685$). Likewise, no association was seen with NNRTI exposure or with combined NNRTI and PI exposure (data not shown).

In this population, the risk of birth defects was not significantly associated with maternal age or IDU as the probable source of HIV acquisition; however, congenital abnormalities were significantly more common in babies born to white women (28 [4.8%] of 578 babies) than in babies born to black women (66 [2.9%] of 2279 babies) ($P = 0.027$). There was no evidence of interaction between ART exposure and these factors. After adjusting for IDU, maternal age, and ethnicity in multivariable logistic regression, there was still no statistically significant association between congenital abnormalities and exposure to ART at any time in pregnancy (OR = 1.7, 95% CI: 0.9 to 3.4; $P = 0.112$), early in pregnancy (OR = 1.2, 95% CI: 0.7 to 1.9; $P = 0.579$), or by different types of early ART (data not shown).

Information on approximately 380 pregnancies ending in termination was also collected, and only 5 abnormalities (<1.5%) were reported: 4 cases of Down syndrome (2 exposed to ART) and 1 case of anencephaly (unexposed). There is thus no evidence of an increased prevalence of abnormalities in this group.

DISCUSSION

It is reassuring that no significantly increased risk of congenital abnormalities was identified among babies born to women taking ART at any time in pregnancy, among those exposed in the first trimester of pregnancy, or according to type of ART. These findings support those of other European studies[11–13] and of the international (predominantly US-based) Antiretroviral Pregnancy Registry.[9,10] Furthermore, the overall congenital abnormality rate of 3.2% in this population is consistent with reported rates of 2% to 3% for a major congenital anomaly in England.[16]

Our finding of an increased risk for infants born to white women compared with those born to black women may be attributable to differences in other maternal characteristics or exposures that are not routinely collected through the surveillance system.

Because the NSHPC depends on complementary obstetric and pediatric reporting systems, most abnormalities are likely to be reported. Our findings are based on comprehensive national surveillance in a population in which virtually all pregnant women have access to maternity services; as such, they are not likely to be substantially affected by case ascertainment or selection bias. In addition, this population includes infants exposed to the full range of drug regimens currently available, some of whom would not be included in cohort studies or clinical trials. The fact that no significantly increased risk of birth defects was observed among infants exposed to this range of regimens is an important finding. Nevertheless, despite the large number of infants reported to date, we cannot exclude a small increased risk of defects, nor are there yet sufficient data to explore less commonly used drugs or drug combinations or subgroups of abnormalities further.

There have been few clinical trials of HAART in pregnancy; however, a substantial and growing number of HIV-infected women are on HAART at conception and in the early weeks of pregnancy. Pregnant women and those who are contemplating pregnancy are likely to continue to be exposed to new and different drug combinations in increasing numbers. Continued vigilance and monitoring of congenital abnormalities in infants born to ART-treated women are essential.

ACKNOWLEDGMENTS

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relies on active reporting from pediatricians through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health and a parallel active reporting scheme involving obstetric respondents (including midwives, obstetricians, and genitourinary physicians) run under the auspices of the Royal College of Obstetricians and Gynaecologists. The authors thank all those who report to the NSHPC and everyone who has completed forms and provided information during the surveillance period. They also thank Professor Marie-Louise Newell for her helpful comments on earlier drafts of this paper.

P. A. Tookey is the coordinator of the study and the guarantor. Janet Masters manages the database and is responsible for data collection along with C. L. Townsend. P. A. Tookey and C. S. Peckham developed the concept of the paper, and C. L. Townsend carried out the data analysis. M. Cortina-Borja provided statistical advice. C. L. Townsend and P. A. Tookey drafted the paper. All authors contributed to the interpretation of the results, commented on all drafts of the paper, and approved the final version.

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Response to Kourtis *et al.* 'Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis'

In a recent meta-analysis, Kourtis *et al.* concluded that overall antiretroviral therapy in pregnancy was not associated with premature delivery, although they reported that longer duration of treatment and regimens that included a protease inhibitor (PI) might increase the risk of prematurity [1]. By contrast, we

subsequently reported a statistically significant 1.5-fold increased risk of prematurity among women on highly active antiretroviral therapy (HAART) with or without a PI, compared with women on monotherapy or dual therapy [2]. In another recent study, Schulte *et al.* reported a similar significant association, but limited to women on HAART with a PI and compared with women on dual therapy (adjusted odds ratio = 1.21) [3].

As Kourtis *et al.* noted, there was a significant degree of heterogeneity between the studies included in their meta-analysis, suggesting that bias or confounding could have been a problem. The studies they included were conducted over different time periods and in quite different populations, and sometimes had different inclusion criteria. It is questionable, therefore, whether a meta-analysis was appropriate.

Furthermore, there is a fundamental problem with the comparison of pregnancies that are exposed and unexposed to antiretroviral therapy. Since the majority of diagnosed HIV-infected women in resource-rich settings are now offered antiretroviral therapy in pregnancy (and very few decline), premature delivery itself is often the reason for not receiving treatment. This could lead to a failure to identify a real association between antiretroviral therapy and prematurity.

Differences in treatment classification could also be a problem; in the meta-analysis, regimens containing two antiretroviral drugs were combined with those containing three or more. Dual therapy is no longer commonly used, as it has lower potency than HAART (three or more drugs, generally from at least two different drug classes). The inclusion of studies where combination therapy consists mainly of dual therapy (e.g. Mandelbrot *et al.* 2001 [4]) rather than HAART could therefore attenuate any association with exposure to more potent combinations of drugs.

Finally, in several of the studies included in the meta-analysis [4–7], only crude prematurity rates were available, and estimates were therefore not adjusted for potential confounders such as maternal injecting drug use, HIV-related symptoms or prior preterm delivery. Since the studies were carried out over different time periods, the baseline characteristics of the women in these different studies and in the different treatment groups are likely to have varied substantially, and adjusted estimates are essential.

Investigation of the association between antiretroviral therapy and prematurity in any single observational study is fraught with difficulties. The potential for bias and/or confounding in such studies means that any meta-analysis needs to be interpreted with caution.

Claire L. Townsend, Mario Cortina-Borja, Catherine S. Peckham and Pat A. Tookey, *MRC Centre of Epidemiology for Child Health, Institute of Child Health, University College London, London, UK.*

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Appendix 2 NSHPC and BPSU data collection forms

Royal College of Obstetricians & Gynaecologists

Q75

NATIONAL STUDY OF HIV IN PREGNANCY

Quarterly Notification Card

This card is for reporting cases first seen between January and March 2008, including pregnancies in previously diagnosed women.

If there are no HIV positive pregnancies to report, please tick the box marked None.

Please complete and return this section of the card

Number of HIV positive pregnancies first seen between January and March 2008 (NB including pregnancies in previously diagnosed women)

None ☐ 1 ☐ 2 ☐ more ☐ specify number

Please give us a reference (e.g. woman's hospital number, date of birth or EDD) which will enable you to identify each case:

Q75

Please note below the hospital number(s) or other identification for cases notified, and **keep this section of the card** for easy reference when you receive a clinical form.

In case of queries, please contact
Janet Masters or Barbara Willey tel: 020 7829 8686

NSHPC confidential pregnancy notification

MREC approval ref: MREC/04/2/009

CONFIDENTIAL
Tick boxes, complete, ring, or delete as appropriate

form date 05/07

Hospital…… Your ref (eg woman's hospital number)……

Woman's date of birth ___/___/___ Previous livebirths ..... stillbirths ..... miscs/terms .....

Ethnic origin ☐ Black African ☐ Black Caribbean ☐ Black other ☐ Oriental
☐ White ☐ Indian Subcontinent ☐ Other or mixed, specify .....

Country of birth…… If not UK/Ireland, date arrived ___/___/____

Current postcode of residence (leave off last letter): ☐☐☐☐ ☐☐■

PREGNANCY LMP ___/___/___ *and/or* EDD ___/___/___

☐ Continuing to term - if continuing, planned mode of delivery: ☐ Vaginal ☐ CS ☐ Not yet decided

☐ Miscarriage } Date of misc/TOP: ___/___/___ at ..... weeks gestation
☐ Termination }

Any congenital abnormality? ☐ No ☐ Yes, please specify.....

PROBABLE SOURCE OF INFECTION

☐ From high prevalence country, specify ..... ☐ Injecting drug use

☐ Infected partner, specify his likely risk factor ..... ☐ Other, specify ……..……..

TIMING OF DIAGNOSIS

Date of first positive test: ___/___/_____ If type 2 only, please tick here ☐

Diagnosed **when**: ☐ During this pregnancy ☐ Before this pregnancy

Diagnosed **where**: ☐ Antenatal ☐ GUM clinic ☐ Other .....

CLINICAL STATUS & DRUG TREATMENT DURING PREGNANCY date of onset (mm/yy):

☐ CDC Stage C disease, date of onset (mm/yy) _____/_____ ☐ Symptomatic, not stage C disease _____/_____

☐ Asymptomatic Details of any symptoms…….....

Was this woman on drug treatment when she became pregnant? ☐ No ☐ Yes Started ___/___/___

If **Yes**, specify drug(s) …….…… Continuing? ☐ No ☐ Yes

……..…… Date stopped ___/___/___

Drug treatment changed or started during pregnancy?

☐ No ☐ Not yet ☐ Declined ☐ Yes, changed or started, details below:

Drug(s) ……..…… Date started:

……..... ___/___/___

MATERNAL TEST RESULTS ***first test results available this pregnancy***

Viral load ..... copies/ml Date ___/___/___ **CD4** no._____ (_____%) Date ___/___/___

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email _____

PLEASE ADD ANY ADDITIONAL INFORMATION OR COMMENTS OVERLEAF

Thank you for your help. Please return this form to: Dr Pat Tookey, RCOG, 27 Sussex Place, Regent's Park, London NW1 4RG.
Telephone NSHPC on 020 7829 8686 if you have any queries or email nshpc@ich.ucl.ac.uk

NSHPC outcome of notified pregnancy

MREC approval ref: MREC/04/2/009

CONFIDENTIAL *form date 05/07*
Tick boxes, complete, ring, or delete as appropriate

Boxes for office use only

Your ref..... Woman's date of birth __/__/__ Hospital of delivery .....

PREGNANCY OUTCOME

Date ___/___/___ Gestation ..... (wks) ☐ Livebirth ☐ Stillbirth ☐ Miscarriage ☐ Termination

Birthweight ..... (kg) ☐ Male ☐ Female Hospital no ..... NHS no .....

Mode of delivery: *If twins, please tick here* ☐ *and write details of second twin overleaf*

☐ Elective CS, reason: ☐ Prevention of mother-to-child transmission ☐ Other, specify .....

☐ Planned vaginal delivery ☐ Unplanned vaginal delivery, reason .....

☐ Emergency CS, specify reason: .....

If emergency CS, what was *planned* mode of delivery? ☐ Vaginal ☐ Elective CS ☐ Not known

ROM: Did membranes rupture before delivery? ☐ No ☐ Yes If yes, duration of ROM .....

Complications: Pregnancy (eg pre-eclampsia)? ☐ No ☐ Yes, specify .....

Perinatal infections? ☐ No ☐ Yes, specify .....

Congenital abnormalities? ☐ No ☐ Yes, specify .....

Postcode at delivery (leave off last letter) ☐☐☐☐ ☐☐■ Paediatrician .....

MATERNAL CLINICAL STATUS AT DELIVERY

If woman has died,

☐ Asymptomatic ☐ Symptomatic, not stage C disease ☐ CDC Stage C disease Date of death ___/___/___

Details .....

DRUG TREATMENT DURING PREGNANCY (continue overleaf if necessary)

Ante-partum treatment? ☐ No ☐ Yes, reason (if known): ☐ prevention of mother-to-child transmission ***only***
☐ maternal health ***and*** prevention of transmission

Antiretrovirals:	date started (or gest week)	date stopped (or gest week)
Drug 1	___/___/___ _____	___/___/___ _____
Drug 2	___/___/___ _____	___/___/___ _____
Drug 3	___/___/___ _____	___/___/___ _____
Drug 4	___/___/___ _____	___/___/___ _____
Drug 5	___/___/___ _____	___/___/___ _____

Any other significant ante-partum drugs (eg PCP prophylaxis, TB treatment, prescribed methodone, illicit drugs)

Drug 1 ..... date ___/___/___ Drug 2 ..... date ___/___/___

Intra-partum antiretroviral treatment?

☐ Intravenous zidovudine (AZT) ☐ None ☐ Additional oral antiretrovirals: .....

Post-partum antiretroviral(s) for **infant**? ☐ Yes, drug(s)..... ☐ No ☐ Not known

MATERNAL TEST RESULTS CLOSE TO TIME OF DELIVERY *just before delivery if possible*

Viral load ..... copies/ml Date ___/___/___ **CD4** no. _____ (_____%) Date ___/___/___

Resistance testing done this pregnancy? ☐ Yes ☐ No ☐ Not known

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email _____

Thank you for your help. Please return this form to: Dr Pat Tookey, RCOG, 27 Sussex Place, Regent's Park, London NW1 4RG.
Telephone NSHPC on 020 7829 8686 if you have any queries or email nshpc@ich.ucl.ac.uk

British Paediatric Surveillance Unit Report Card

NOTHING TO REPORT ☐ 2005-06

CODE No [ ]

Specify in the box number of cases seen

- ☐ AIDS/HIV
- ☐ Congenital rubella
- ☐ Progressive Intellectual & Neurological Deterioration
- ☐ Neonatal Herpes Simplex Virus (HSV) Infection
- ☐ Medium chain acyl CoA dehydrogenase deficiency
- ☐ Thyrotoxicosis in childhood
- ☐ Non-type 1 diabetes (upto 17years)
- ☐ Early onset eating disorder in children <13 years
- ☐ MRSA
- ☐ Scleroderma
- ☐ Malaria in childhood

NSHPC confidential paediatric notification

LONDON MREC/04/2/009

office use only *May 2005*

CSTU	MSTU	SU	PAED	HOSP

Paediatrician _____ **Hospital** _____

CONFIDENTIAL Please complete this form as far as you can, even if you do not have all details requested

A PAEDIATRIC DETAILS

NHS no ..... Hospital no ..... Initials ..... Soundex .....

Date of birth ___/___/___ ☐ Male ☐ Female Home postcode ***(leave off last letter)*** ☐☐☐☐ ☐☐■

Ethnic origin ☐ White ☐ Black African ☐ Black Caribbean ☐ Black other
☐ Indian Subcontinent ☐ Oriental ☐ Other or mixed, specify .....

Born in ☐ UK/Ireland Hospital of birth ..... Home postcode at birth ***(leave off last letter)*** ☐☐☐☐ ☐☐■
or ☐ Abroad Country of birth ..... and date arrived in UK/Ireland ___/___/___

B HOW WAS THIS CHILD IDENTIFIED AS INFECTED OR AT RISK OF INFECTION?

☐ Mother known to be infected in pregnancy ☐ Child symptomatic
☐ Mother/other family member found to be infected (specify relationship) .....
☐ NK ☐ Other, specify .....
Date of child's first lab investigation ___/___/___ ☐ not yet done ☐ tests refused ☐ NK
If you are aware of *siblings* reported to us, please give dates of birth or other ref: .....

C PERINATAL DETAILS

Mode of delivery ☐ vaginal ☐ elective CS ☐ emergency CS ☐ NK **Gestation** ..... **Birthweight** .....

Any perinatal infections? ☐ No ☐ Yes, specify .....
Any congenital abnormalities? ☐ No ☐ Yes, specify .....
Any other problems? ☐ No ☐ Yes, specify .....

Anti-retroviral treatment for mother and/or baby to reduce risk of vertical transmission? ☐ No ☐ Yes, specify below
Antenatally? ☐ NK ☐ No ☐ Yes, specify .....
Intrapartum? ☐ NK ☐ No ☐ Yes, specify .....
Post-partum (baby)? ☐ NK ☐ No ☐ Yes, specify .....

Was the child breastfed? ☐ No ☐ Yes, and breastfed for how long? (wks) ..... ☐ NK if breastfed

D PROBABLE SOURCE OF INFECTION

1. Exposed to maternal infection? ☐ Yes, please give *mother's* details below ☐ No, go to question 2 below ☐ NK

a) Mother's date of birth ___/___/___ b) No. of *previous* livebirths..... stillbirths..... miscarriages/terms.....
c) Mother's country of birth ..... and if not UK/Ireland, date arrived ___/___/___
d) Mother diagnosed ☐ after the birth of this child ☐ while pregnant with this child ☐ before this pregnancy
e) Maternal infection probably acquired ☐ in UK/Ireland ☐ abroad, specify ..... ☐ NK where and likely exposure (tick all that apply)
☐ injecting drug use ☐ transfusion recipient
☐ sexual exposure, specify partner's probable risk factors if known .....
☐ mother to child transmission ☐ no information on mother's exposure

2. Other exposure risk for child? ☐ No ☐ Yes, please give details
☐ blood/blood products abroad, please specify country and year .....
☐ sexual exposure ☐ other, please specify.....

E INFECTION STATUS & LABORATORY INVESTIGATIONS

Do you consider this child to be ☐ infected ☐ not infected ☐ indeterminate (definitions on next page)

If indeterminate and further laboratory investigations refused, please tick ☐

Any evidence of type 2 infection? ☐ No ☐ Yes

	pos	neg	sample date	pos	neg	sample date
Antibody	☐	☐	___/___/___	☐	☐	___/___/___
PCR	☐	☐	___/___/___	☐	☐	___/___/___
Other test	☐	☐	___/___/___	☐	☐	___/___/___

specify test.....

Viral load ..... copies/ml (..... log_{10}) type of test ..... date ___/___/___

CD4.....% no. ..... CD8.....% no. ..... Total lymphocytes no. ..... ___/___/___

F THERAPY (tick all that apply and give brief details)

PCP prophylaxis? ☐ No ☐ Yes, specify .....date started ___/___/___

Antiretroviral treatment for **infected** child? ☐ Not applicable (uninfected) ☐ No ☐ Yes, specify drugs below

..... date treatment started ___/___/___

Child enrolled in clinical trial? ☐ No ☐ Yes, trial .....trial no..... date enrolled ___/___/___

G CLINICAL DETAILS

Date of last examination ___/___/___ *and, if taken at that time:* Weight (kg) ..... Height (cm) .....

Has the child had any CDC stage C symptoms? ☐ No ☐ Yes (See back page for definitions)

	Comments	**Diagnosis** Presumptive / Definitive	**Date** mm/yy
Opportunistic infections, specify	.....	☐ / ☐	___/___
Severe, symptomatic LIP	.....	☐ / ☐	___/___
Severe recurrent bacterial infection	.....	☐ / ☐	___/___
Severe failure to thrive	.....	☐ / ☐	___/___
Encephalopathy, specify	.....	☐ / ☐	___/___
Neoplasms, specify	.....	☐ / ☐	___/___

Has the child had any other symptoms related to the infection? ☐ No ☐ Yes (See next page for definitions)

Symptoms/signs	**Initial onset** (mm/yy)	**Comments**
Mild/asymptomatic LIP	___/___	.....
Severe bacterial infection	___/___	.....
Failure to thrive	___/___	.....
Regression of milestones	___/___	.....
Other related symptoms, specify	___/___	.....

Any other serious infections or conditions? ☐ No ☐ Yes, specify .....

H FOLLOW UP STATUS

Date of last contact ___/___/___ ☐ Alive ☐ Lost to follow up ☐ Known to have left UK/Ireland

☐ Dead, date of death ___/___/___ and if dead

Certified cause of death: a) disease or condition directly leading to death .....

b) secondary cause(s) .....

Post-mortem? ☐ Not done ☐ Done. Please attach a copy if possible.

Completed by: Name _____ Position_____ Date ___/___/___

Tel no _____ Email_____

Thank you for completing this form. Please return it to: Surveillance Studies Group, Centre for Paediatric Epidemiology & Biostatistics, Institute of Child Health, 30 Guilford Street, London WC1N 1BR. Call us with any queries on 020 7829 8686 or email nshpc@ich.ucl.ac.uk

Thank you for completing the attached form. Please return it in the freepost envelope to:
Surveillance Studies Group, MRC Centre of Epidemiology for Child Health, Institute of Child Health, 30 Guilford St, London WC1N 1BR.

If you have any queries phone us on 020 7829 8686 or email nshpc@ich.ucl.ac.uk.

Please complete this box and keep this page for your own records to help identify the child when you receive a follow-up form

Child's name or other identification .....

Hospital number ..... Study number (CSTU) .....

INFECTION STATUS

INFECTED
a) definitive
1. Child has Stage C disease (see definitions overleaf)
2. The detection of virus by PCR (at any age) on two separate specimens taken at different times
3. Antibody positive after the age of 18 months, or at any age if not born to an infected woman

b) presumptive
The detection of virus by PCR (at any age) on one occasion

NOT INFECTED
a) definitive
Any one of the following and no evidence (viral, immunological or clinical) of infection:

1. One negative antibody test after the age of 12 months
2. Two consecutive negative antibody tests on separate samples taken at different times in children under 12 months
3. Two separate, consecutive, negative PCR results after one month of age – at least one of these to be after 3 months of age
4. One negative PCR result and one negative antibody test on separate occasions after the age of 3 months

b) presumptive (in a non-breastfed child)
Either of the following and no evidence (viral, immunological or clinical) of infection:

1. One negative antibody test under the age of 12 months
2. One negative PCR after the age of one month

Indeterminate
A child born to an infected woman where the child's own infection status is not yet determined

Definitions of specific manifestations of infection requested

Manifestation	Definition
Asymptomatic LIP* (see overleaf for definition of LIP)	CXR abnormalities only; no respiratory signs or symptoms
Severe bacterial infection	Single severe bacterial infection (state how diagnosed)
Failure to thrive	Failure to thrive, not yet meeting definition overleaf
Regression of developmental milestones	Consistent regression over at least 3 months

P.T.O. for definitions of Stage C indicator diseases

Stage C indicator diseases

Abbreviated from the CDC Classification 1994

Diseases	Definitions
Candidiasis Coccidioidomycosis Cryptococcosis Cryptosporidiosis Cytomegalovirus Herpes simplex virus Histoplasmosis Isosporiasis Atypical mycobacterium Mycobacterium tuberculosis Pneumocystis carinii pneumonia Progressive multifocal leukoencephalopathy Toxoplasmosis	Oesophageal or respiratory tract Disseminated or extrapulmonary Extrapulmonary Chronic intestinal with diarrhoea for >1 month Disseminated with onset >1 month of age Disseminated with onset >1 month of age Disseminated or extrapulmonary Chronic intestinal with diarrhoea for >1 month Disseminated at site other than or in addition to lungs, skin, cervical or hilar lymphadenopathy Disseminated or extrapulmonary Pneumonia Of the brain with onset >1 month of age
Severe Lymphocytic Interstitial Pneumonia (LIP)*	Defined as any of: Respiratory failure, oxygen dependence, severe exercise intolerance with oxygen desaturation
Severe recurrent bacterial infection	(Any combination of at least 2 within a 2 year period) septicaemia, pneumonia, meningitis, bone or joint infection, abscess of internal organ or body cavity
Severe failure to thrive/wasting syndrome	Crossing at least two percentile lines (97, 90, 75, 50, 25, 10, 3) on the growth chart (eg 90th to 50th or 50th to 10th) or less than the 3rd percentile and continuing to deviate downwards from it over a 3 month period, or more than 10% loss of body weight in older child *plus* a) chronic diarrhoea >30 days OR b) documented intermittent or constant fever >30 days
Encephalopathy	At least one of the following progressive findings for at least two months in the absence of a concurrent illness that could explain the findings: a) Failure to attain, or loss of, developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests b) Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or by brain atrophy demonstrated by computerised tomography or magnetic resonance imaging (serial imaging for children <2 years of age) c) Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia or gait disturbance
Kaposi's Sarcoma Lymphoma Immunoblastic Sarcoma	CNS or small cell, non-cleaved (Burkitt or non-Burkitt)

***Definition of LIP:** Diffuse bilateral reticulonodular interstitial infiltrates with or without hilar lymphadenopathy present on chest x-ray for at least 2 months and unresponsive to antimicrobial therapy (presumptive); or histologically confirmed pneumonitis with diffuse peribronchiolar infiltration of lymphocytes and plasma cells, without identifiable pathogens (definitive). Other causes of interstitial infiltrates such as TB, Pneumocystis, CMV should be excluded.

Definitive diagnosis: microscopy (histology or cytology); culture; antigen detection

Presumptive diagnosis: characteristic clinical presentation, supported by investigations other than microscopy or culture and after exclusion of other causes in the differential diagnosis

NSHPC follow-up to establish infection status

MREC ref: MREC04/2/009

office use only *November 2007*

CSTU	MSTU	SU	PAED	HOSP

Paediatrician ..... Hospital .....

CONFIDENTIAL Please complete this form as far as you can, even if you do not have all details requested

Please complete or amend these child details

Date of birth ___/___/___ ☐ Male ☐ Female Initials ..... soundex .....

Hospital no..... NHS no..... Current home postcode (**leave off last letter**) ☐☐☐☐ ☐☐■

The last report we had on this child related to examination on ___/___/___ when his/her **infection status had not yet been confirmed**. If you have more recent information, please complete all sections of this form.

If you have not seen this child since the last report please tick here ☐, complete the section on **INFECTION STATUS**, provide any test results *not previously reported* and complete the section on **FOLLOW UP STATUS.**

INFECTION STATUS & LABORATORY INVESTIGATIONS

Do you consider this child to be ☐ infected ☐ not infected ☐ indeterminate (definitions overleaf)

Please provide date of sample and ring type of test and result for all diagnostic tests since ___/___/___

	sample date	type of test	result		sample date	type of test	result
1.	___/___/___	antibody / PCR	+ / -	4.	___/___/___	antibody / PCR	+ / -
2.	___/___/___	antibody / PCR	+ / -	5.	___/___/___	antibody / PCR	+ / -
3.	___/___/___	antibody / PCR	+ / -	6.	___/___/___	antibody / PCR	+ / -

CLINICAL DETAILS

Any other serious infections or conditions? ☐ No ☐ Yes, specify .....

.....

FOLLOW UP STATUS

Date of last contact ___/___/___ ☐ Still in follow-up at this unit ☐ Discharged (uninfected child)

☐ Follow-up elsewhere, please provide contact details .....

.....

☐ Lost to follow up ☐ Known to have left UK/Eire ☐ Dead, date of death ___/___/___ and if dead

Certified cause of death a) disease or condition directly leading to death .....

b) secondary cause(s) .....

Post-mortem? ☐ Not done ☐ Done (please attach a copy if possible)

Completed by: Name _____ Position_____ Date ___/___/___

Tel no _____ Email_____

Thank you for completing this form. Please return it to: Surveillance Studies Group, Centre for Paediatric Epidemiology & Biostatistics, Institute of Child Health, 30 Guilford Street, London WC1N 1BR. Call us with any queries on 020 7829 8686 or email nshpc@ich.ucl.ac.uk

INFECTION STATUS

INFECTED
a) definitive
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3. Antibody positive after the age of 18 months, or at any age if not born to an infected woman

b) presumptive
The detection of virus by PCR (at any age) on one occasion

NOT INFECTED
a) definitive
Any one of the following and no evidence (viral, immunological or clinical) of infection:

1. One negative antibody test after the age of 12 months
2. Two consecutive negative antibody tests on separate samples taken at different times in children under 12 months
3. Two separate, consecutive, negative PCR results after one month of age – at least one of these to be after 3 months of age
4. One negative PCR result and one negative antibody test on separate occasions after the age of 3 months

b) presumptive (in a non-breastfed child)
Either of the following and no evidence (viral, immunological or clinical) of infection:

1. One negative antibody test under the age of 12 months
2. One negative PCR after the age of one month

Indeterminate
A child born to an infected woman where the child's own infection status is not yet determined

New follow up details if appropriate or any other comments:

Appendix 3 ECS data collection forms

PERINATAL INFORMATION

Centre
Mothers Study Number
Child Study Number
Child's date of birth (day, month, year)
Sex (M, F)
Gestational age (weeks)
Birthweight (gm)
OFC (cm

Hospital where delivery took place .....
Obstetrician (initals) .....

Antiretroviral therapy during labour/delivery Y/N

If yes, which drug? .....Orally / IV?

Delivery

Caesarean Section: Elective (1), Emergency (2)
If Caesarean Section, reason.....
Vaginal: Spontaneous (3), vacuum (4), forceps (5)
Presentation: breech (Y/N)
Duration of labour 1st stage (if known).....
Duration of labour 2nd stage (if known) .....
Time from rupture of membranes to delivery (if known).....
Scalp Electrodes (Y/N)
Episiotomy or vulvovaginal tear (Y/N)

Perinatal Problems (Y/N). Specify Details:

Hepatomegaly .....
Splenomegaly .....
Drug Withdrawal Symptoms .....
Thrombocytopenic Purpura .....
Infection: suspected (1) confirmed (2) .....
Transfusion ..... *
Congenital Abnormalities ..... *
Other .....

Disposition

with parents (1) fostered (2) adopted (3)
remained in hospital (4) other (5) ..... *
if remained in hospital, say why: .....

Feeding: breast (1) bottle (2) breast and bottle (3)
was breast feeding tried and abandoned? Y/N

Died? Y/N
Date of death: (day/month/year)
Postmortem results, if available ..... *
.....

Take sample required; Please record laboratory results on yellow form

9 2

ECS3
INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

MATERNAL INFORMATION AT DELIVERY

Centre
Mothers Study Number
Child Study Number

Mother's date of birth (day, month, year)
Country of birth .....

Marital Status

Single (1), Married (2), Divorced, Separated, Widowed (3), Cohabiting (4)

Ethnic Group

Asian (1), White (2), Black (3), Oriental (4), Other (5)
Age when leaving full-time education, years .....

Obstetric History

Number of previous livebirths .....
Number of previous stillbirths .....
Number of previous miscarriages .....
Number of previous terminations .....

Mothers Risk Group

History of intravenous Drug Abuse (Y/N)
Trimester of last use: pre-conception (0), 1st (1), 2nd (2), 3rd (3), unknown (9)
Needle sharing? never (1) past (2) present (3) unknown (9)
Sexual partner of Bisexual (Y/N)
Sexual partner of Haemophiliac (Y/N)
Sexual partner of Intravenous Drug Abuser (Y/N)
Sexual partner of Other high risk group (Y/N)
(Specify) .....
Other .....

Mothers HIV History

Date of first HIV+ test (day, month, year)

Current clinical status

Current HIV staging (CDC) .....
Specify symptoms .....
Date of onset .....

Details of treatment during pregnancy

Has the woman received any antiretroviral therapy at any time during this pregnancy? Y/N
Please give details of both ART and other prophylaxis (eg. TMP-SMX)

Drug	Date started	Date stopped	Currently taken? (yes/no)

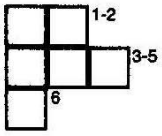
ECS 3
PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

Page 2

MATERNAL INFORMATION

Laboratory investigations during pregnancy and at delivery:

Centre Number
Mothers Study Number
Child Study Number



Virology

	Date:	Date:	Date:
HIV-DNA PCR	Pos / Neg	Pos / Neg	Pos / Neg

HIV-RNA PCR	copies/ml	copies/ml	copies/ml
Sample type	Plasma / Serum	Plasma / Serum	Plasma / Serum
Assay used			

Other laboratory investigations

	Date:	Date:	Date:
Total lymphocytes			
CD4 (10^9/litre)			
CD8 (10^9/litre)			
IgG (gm/litre)			
IgA (gm/litre)			
IgM (gm/litre)			
p24 Ag			
HIV Elisa			

INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS
MULTI CENTRE EEC STUDY

MEDICAL EXAMINATION

Please circle or complete as appropriate

Assessment at : 3w, 6w, 3m, 4.5m and 6 m

Centre 1-2
Mothers Study Number 3-5
Child Study Number 6
Date of Examination 7-12
Weight (kg) 13-16
Height (cm) 17-20
OFC (cm) 21-23

24 **For office use only**

25 **Recurrent fever** of unknown origin requiring medical attention .....Y/N
26 **Chronic or Recurrent diarrhoea** requiring medical attention .....Y/N
27 Specify organism .....
Bacterial infection .....Y/N
28-30 If yes, specify:
31-33 Septicaemia, Meningitis, Urinary tract infection, Pneumonia, Other .....
Communicable Disease .....Y/N
34-35 Measles (1) Mumps (2) Rubella (3) Varicella (4) Zoster (5) Other (6) .....
Complications .....
36-38 **Skin Infection** requiring medical attention .....Y/N
Staph (1) Strep (2) Herpes (3) Candida (4) Other (5) .....
39 **Non-infectious skin eruption** .....Y/N
40 Petechiae/Purpura (1) Eczema (2) Kaposi Sarcoma (3) Other (4) .....
41-43 **Palpable Lymph Nodes** .....Y/N
44-46 Axillary (1) Postoccipital (2) Cervical (3) Inguinal (4) Epitrochlear (5) Other (6)
47 **Chronic parotid swelling** .....Y/N
48 **Oral Candida** persistent or recurrent despite therapy .....Y/N
Upper respiratory tract infection .....Y/N
49-50 Chronic otitis media (1) Sinusitis (2) Chronic purulent rhinitis (3) Other (4).....
Lower respiratory tract disease confirmed by X-ray.....Y/N
Lymphocytic intersitial pneumonitis or Pulmonary lymphoid hyperplasia (1)
51-53 Pneumonia (2) Bronchiolitis (3) Other (4) .....
specify organism, if known.....
54 **Opportunistic Infection** .....Y/N
PCP (1) CMV (2) Toxo (3) Candida (4) Mycobacterium (5) Other (6) .....
55 **Hepatomegaly**.....Y/N
56 **Splenomegaly**.....Y/N

7 1 57-58

Please circle or complete as appropriate

Medical Examination

Date of Examination ___ / ___ / ___

Centre 1-2
Mothers Study Number 3-5
Child Study Number 6 7

For office use only

Neurological abnormality ..... Y/N 8-10
encephalopathy (static/progressive) (1) 11-13
seizures (2) paresis (3) pathologic reflexes (4) increased tone (5)
decreased tone (6) abnormal gait (7) other (8) 14-16

Other Findings on exam Specify ..... Y/N 17

Developmental Asessment

Gross motor	Pass (1) Fail (2) Suspicious (3)	18
Fine motor/adaptive	Pass (1) Fail (2) Suspicious (3)	19
Language	Pass (1) Fail (2) Suspicious (3)	20
Personal/social	Pass (1) Fail (2) Suspicious (3)	21

Loss of developmental milestones ..... Y/N
specify 22-23

Neonate

Has the baby received any anti-retroviral therapy to reduce
the risk of vertical transmission? ..... Y/N 24
If yes: which drug(s)? 25-26
for how long? 27

Treatment

Has this child been enrolled in an anti-retroviral treatment trial ..... Y/N 28
If yes: which trial? 29-31
Current treatment (excluding the above)
IVGG, AZT, DDi, Other 32-36 37-41

Hospital Admission(s) ..... Y/N 42
(Indicate dates of admission/discharge and diagnoses for each hospitalization)
..... 43-46
..... 47-50

Immunisations given since last visit ..... Y/N
DPT (1) DT(2) Oral Polio (3) Killed Polio (4) Measles (5) MMR (6)
Hepatitis B (7) Other (8) 51-52
Abnormal reactions ..... Y/N 53-54 55

Child care

mother / father / other relative / fostered / adopted / hospital / institution

Breast Feeding ..... Y/N 56
If stopped, when 57-58

Health of Mother .....
Is mother alive / dead? 59
if dead, was death HIV-related? ..... Y/N 60
cause of death 61
Mother's current HIV staging (CDC) 62-63
defining symtoms 64-68
date of diagnosis 69-73
current treatment? 74-75

8 2 76-77

ECS.1

PROSPECTIVE STUDY OF CHILDREN BORN TO HIV +VE MOTHERS

<u>Assessment:</u> 9, 12, 18 and 24 months; thereafter annually for antibody -ve, uninfected children and 6-monthly for infected children

Please circle or tick as appropriate

Centre number 1-3
Mother Study number 4-6
Child Study number 7
Weight (kg) 8-11
Height (cm) 12-15
Head circumference (cm) 16-18

Is child alive? Y/N 19 **For office use only**
Date of assessment (day, month, year) 20-25

Name of paediatrician (initials) 26-27

Is this child HIV infected? . . . . . Y/N 28
Has this child developed AIDS? (CDC def) . . . . . Y/N 29
If AIDS has been diagnosed since previous report,
specify date of diagnosis 30-35
AIDS indicator disease 36-38

Care
mother / father / other relative / fostered / adopted / hospital / institution 39

Is mother alive / dead?
if dead, was death HIV-related? . . . . . Y/N 40
cause of death 41

Preschooling/Schooling
Does this child require special educational provisions . . . . . Y/N 42
if yes, specify 43-44

Treatment
Has this child been enrolled in an anti-retroviral treatment trial . . . . . Y/N 45
if yes, which trial? 46-48
Current treatment (excluding the above) 49-53
Intravenous gammaglobulin/AZT/DDi/other, specify 54-58
. . . . . .

Communicable diseases . . . . . Y/N 59
if yes, specify: measles / whooping cough / varicella / tuberculosis / mumps / zoster

G 2 1 60-62

ECS .1 **(page 2)** Centre ..... Mother ..... Child ..... Date ...../...../.....

Oral Candida since last visit (persisting > 2m or recurring despite therapy) Y / N
if yes, date on onset (day, month, year) .....

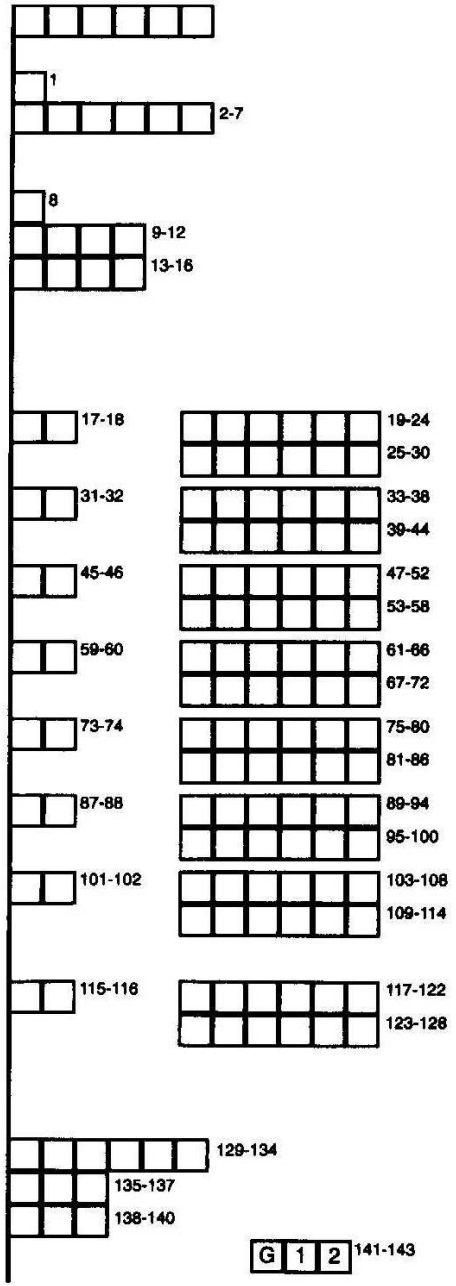
Hospital admission(s) Y / N
(indicate dates of admission/ discharge and diagnoses for each hospitalization)
.....

Since the last visit, has this child had any of the following abnormalities:

	yes/no	date	clinical presentation	method of diagnosis	diagnosis
renal	Y / N	.....			
hepatic	Y / N	.....			
gastro-intestinal	Y / N	.....			
cardio-vascular	Y / N	.....			
central nervous system	Y / N	.....			
respiratory	Y / N	.....			
malignancy	Y / N	.....			
other, specify	Y / N	.....			

Please complete this section, if the child has died

Date of death .....
Cause of death .....
Post mortem results .....



PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

Centre 1-2
Mothers Study Number 3-5
Child Study Number 6

LABORATORY INVESTIGATIONS

Assessment at:
0-7 days, 3w, 6w, 4.5m, 6m, 9m, 12m, 18m, 24m, and then annually if child presumed not infected, or 6 monthly if infected

Ring findings and specify as appropriate:

for office use only

Date blood drawn: _____ / _____ / _____ 7-12
day month year

HIV / ELISA +/- Specify system used 13-14
antibodies 15-16

Western blot +/- 17-18

Virus culture
+/- Specify identification system(s) 19-20
+/- Specify identification system(s) 21-22

Viral load
DNA - PCR 23-24
RNA - PCR 25-26

Antigen assay +/- 27-29
Specify identification system .....

Other tests (eg IVAP, PCR, IgM) Specify method and result
+/- 30-32
+/- 33-35

IgG (gm/litre) 36-38
IgA (gm/litre) 39-41
IgM (gm/litre) 42-44
T4 (10^9/litre) 45-48
T8 (10^9/litre) 49-52
Absolute lymphocyte (10^9/litre) 53-56
Neutrophil (10^9/litre) 57-60
Platelet (10^9/litre) 61-64
Haemoglobin (gm/dl) 65-67

Toxo IgG Latex (at 9 months to exclude congenital infection) (+/-) 68
Tetanus IgG (at least 1 month after third DT/DPT) 69-71
CMV IgG (+/-) 72

252

8 1 73-74

Appendix 4 PSD data collection forms

DEPARTMENT OF HEALTH & HUMAN SERVICES / PUBLIC HEALTH SERVICE / CENTERS FOR DISEASE CONTROL AND PREVENTION

PEDIATRIC HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION: INITIAL FORM

FORM NUMBER:	DATE THIS FORM COMPLETED:	HARSO:	IF DEAD: DATE OF DEATH	IF ALIVE: LAST PATIENT CONTACT
[0] Initial	Mo. Day Yr.		Mo. Day Yr.	Mo. Yr.

I./II. BASIC PATIENT INFORMATION

PATIENT NUMBER:	DATE OF BIRTH: Mo. Day Yr.	SOUNDEX NAME CODE:	HEALTH DEPARTMENT: State City/County	SEX:
				[1] Male [2] Female

RACE/ETHNICITY:
[1] White (not Hispanic) [2] Black (not Hispanic) [3] Hispanic
[4] Asian/Pacific Islander [5] American Indian/ Alaskan Native
[8] Other: _____ [9] Not specified

COUNTRY OF BIRTH
[1] U.S. [2] U.S. Dependencies and Possessions (including Puerto Rico)
(specify): _____
[8] Other (specify): _____ [9] Unknown

RESIDENCE AT DIAGNOSIS OF HIV INFECTION/EXPOSURE:
State: _____ City: _____
Zip: _____ County: _____

HOSPITAL WHERE DIAGNOSIS OF HIV CONSIDERED:
Name: _____
State: _____ City: _____

DATE OF INITIAL EVALUATION FOR HIV INFECTION: Mo. Yr.

REASON FOR INITIAL EVALUATION : (check all that apply)

	Yes	No	Unk.
• Child had potential exposure to HIV	1	0	9
• Child had symptoms suggestive of HIV	1	0	9
• Found in routine screening	1	0	9

FOR PERINATAL CASES:

	Yes	No	Unk.
• Was mother diagnosed with HIV (or AIDS) before childs birth?	1	0	9
• Did mother have HIV symptoms at the time of child's birth?	1	0	9

PRENATAL CARE?

Yes	No	Unk.
1	0	9

This child's biologic mother had: (check all that apply)

	Yes	No	Unk.
• Injected nonprescription drugs	1	0	9
• Heterosexual relations with:			
• Person who injected nonprescription drugs	1	0	9
• Bisexual man	1	0	9
• Male with hemophilia/coagulation disorder	1	0	9
• Transfusion recipient with documented HIV infection	1	0	9
• Transplant recipient with documented HIV infection	1	0	9
• Male with AIDS or documented HIV Infection, risk not specified	1	0	9
• Received a transfusion of blood/blood components (other than clotting factor)	1	0	9
• Received transplant of tissue/organs or artificial insemination	1	0	9
• Been diagnosed as having AIDS or documented HIV infection	1	0	9

Before the diagnosis of HIV Infection, this child had: (check all that apply)

	Yes	No	Unk.
• Received clotting factor for coagulation disorder?	1	0	9
• If yes, specify disorder: [1] Factor VIII (Hemophilia A) [2] Factor IX (Hemophilia B) [8] Other: (specify): _____			
• Received a transfusion of blood/blood components (other than clotting factor)	1	0	9
FIRST Mo. Yr. LAST Mo. Yr.			
• Received transplant of tissue/organs	1	0	9
• Sexual contact with a male	1	0	9
• Sexual contact with a female	1	0	9
• Injected nonprescription drugs	1	0	9
• Other (specify): _____	1	0	9

PERINATAL CASES ONLY:

MOTHER WAS BORN IN:
[1] U.S. [2] U.S. Dependencies and Possessions (including Puerto Rico)
(specify): _____
[8] Other (specify): _____ [9] Unknown

FATHER WAS BORN IN:
[1] U.S. [2] U.S. Dependencies and Possessions (including Puerto Rico)
(specify): _____
[8] Other (specify): _____ [9] Unknown

RACE/ETHNICITY OF MOTHER:
[1] White (not Hispanic) [2] Black (not Hispanic) [3] Hispanic
[4] Asian/Pacific Islander [5] American Indian/ Alaskan Native
[8] Other: _____ [9] Not specified

RACE/ETHNICITY OF FATHER:
[1] White (not Hispanic) [2] Black (not Hispanic) [3] Hispanic
[4] Asian/Pacific Islander [5] American Indian/ Alaskan Native
[8] Other: _____ [9] Not specified

OTHER INFORMATION ON MOTHER: (check all that apply)

	Yes	No	Unk.
• History of crack use	1	0	9
• History of other street drug use (non-IV)	1	0	9
• Has mother received payment or drugs for sex?	1	0	9

Information in the surveillance system that would permit identification of any individual on whom a record is maintained, is collected with a guarantee that it will be held in confidence, will be used only for the purposes stated in the assurance in the protocol, and will not otherwise be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 USC 242m).

III. MEDICAL HISTORY OF CHILD

PATIENT NUMBER: ☐☐☐☐☐☐☐☐ FORM NUMBER: 0

BIRTH HISTORY:

Hospital: _____ City: _____ State: ☐☐

Birthweight: ☐☐☐☐ (grams)

Type: 1 Single 2 Twin 3 Triplet 9 Unk.

Delivery: 1 Vaginal 2 Caesarean 9 Unk.

Gestational age: 1 Full-term 2 Premature ☐☐ Weeks: (99=Unk.)

Withdrawal symptoms: Yes 1 No 0 Unk. 9

Urine toxic screen Pos. 1 Neg. 0 Not Done 2 Unk. 9

Nursery stay: 1 <7 days 2 7-30 da 3 >30 days 9 Unk.

Chronic underlying disease: (ICD9 Code) ☐☐☐☐☐ _____

Has child ever been hospitalized? Yes 1 No 0 Unk. 9

Total number of admissions since birth admission: ☐☐ (99=Unk.)

Latest weight (Kg) (leave blank if Unk.) ☐☐.☐ Mo. ☐☐ Yr. ☐☐

Any signs/symptoms thought related to HIV? Yes 1 No 0 Unk. 9

Did mother receive zidovudine during pregnancy? Yes 1 No 0 Unk. 9

If yes, what week of pregnancy was zidovudine started? Weeks: ☐☐ (99=Unk.)

Did mother receive zidovudine during labor/delivery? Yes 1 No 0 Unk. 9

Did mother receive any other Anti-retroviral medication during pregnancy? Yes 1 No 0 Unk. 9

If yes, specify: _____

IV. DISEASES INDICATIVE OF AIDS (check all that apply)

DISEASE	Diagnosis* Def.	Diagnosis* Pres.	Date** Mo.	Date** Yr.
Bacterial infections, multiple or recurrent	1	NA	☐☐	☐☐
Candidiasis, bronchi, trachea, or lungs	1	NA	☐☐	☐☐
Candidiasis, esophageal	1	2	☐☐	☐☐
Coccidioidomycosis, disseminated or extrapulmonary	1	NA	☐☐	☐☐
Cryptococcosis, extrapulmonary	1	NA	☐☐	☐☐
Cryptosporidiosis, chronic intestinal (>1 mo. duration)	1	NA	☐☐	☐☐
Cytomegalovirus disease (other than in liver, spleen, or nodes) onset at >1 mo. of age	1	NA	☐☐	☐☐
Cytomegalovirus retinitis (with loss of vision)	1	2	☐☐	☐☐
HIV encephalopathy	1	2	☐☐	☐☐
Herpes simplex: chronic ulcer(s) (>1 mo. duration); or pneumonitis or esophagitis onset at >1 mo. of age	1	NA	☐☐	☐☐
Histoplasmosis, disseminated or extrapulmonary	1	NA	☐☐	☐☐
Isosporiasis, chronic intestinal (>1 mo. duration)	1	NA	☐☐	☐☐
Kaposi's sarcoma	1	2	☐☐	☐☐
Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia	1	2	☐☐	☐☐
Lymphoma, Burkitt's (or equivalent term)	1	NA	☐☐	☐☐
Lymphoma, immunoblastic (or equivalent term)	1	NA	☐☐	☐☐
Lymphoma, primary in the brain	1	NA	☐☐	☐☐
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary	1	2	☐☐	☐☐
M. tuberculosis, disseminated or extrapulmonary (Complete Supplementary Form)	1	2	☐☐	☐☐
Mycobacterium, of other species or unidentified species, disseminated or extrapulmonary	1	2	☐☐	☐☐
Pneumocystis carinii pneumonia	1	2	☐☐	☐☐
Progressive multifocal leukoencephalopathy	1	NA	☐☐	☐☐
Toxoplasmosis of brain, onset at >1 mo. of age	1	2	☐☐	☐☐
Wasting syndrome due to HIV	1	NA	☐☐	☐☐

*Def. = definitive diagnosis Pres. = presumptive diagnosis ** Record the earliest date of diagnosis

V. BACTERIAL INFECTIONS

SERIOUS BACTERIAL INFECTIONS: (Note each separately)

	DIAGNOSIS	DX Code	Def.*	Pres.**	Mo.	Yr.	ORGANISM	SITE
1.	_____	☐☐	1	2	☐☐	☐☐	_____	☐
2.	_____	☐☐	1	2	☐☐	☐☐	_____	☐
3.	_____	☐☐	1	2	☐☐	☐☐	_____	☐
4.	_____	☐☐	1	2	☐☐	☐☐	_____	☐
5.	_____	☐☐	1	2	☐☐	☐☐	_____	☐
6.	_____	☐☐	1	2	☐☐	☐☐	_____	☐

DX CODE:	(01) meningitis; (02) sepsis; (03) bacterial pneumonia; (04) osteomyelitis; (05) septic arthritis; (06) abscess of internal organ; (07) acute mastoiditis; (08) purulent sinusitis; (09) epiglottitis; (10) adenitis; (11) cellulitis; (12) pyelonephritis; (13) UTI; (88) other
ORGANISM SITE:	(1) CSF; (2) blood; (3) other normally sterile body fluid; (8) other

*DEFINITIVE (Def.): specific bacterial etiology. **PRESUMPTIVE (Pres.): bacterial etiology suspected but no organism isolated.

VI. DISEASES NOT IN CASE DEFINITION

PATIENT NUMBER: | | | | | | | | | | FORM NUMBER: 0

NON-SPECIFIC FINDINGS FOR >2 MONTHS: (Subclass A)

	Yes	No	1 Month
• Fever, intermittent or constant	1	0	8
• "Failure to thrive" or falling off growth curve	1	0	
• Weight loss of more than 10% of baseline	1	0	
• Chronic diarrhea	1	0	8
• Recurrent diarrhea (2 episodes of diarrhea with dehydration within a 2 month period)	1	0	
• Lymphadenopathy (0.5 cm at 2 sites; bilateral adenopathy = 1 site)	1	0	8
• Hepatomegaly	1	0	
• Splenomegaly	1	0	
• Parotid gland enlargement	1	0	

PROGRESSIVE NEUROLOGIC DISEASE: (Subclass B) (including children not meeting HIV encephalopathy criteria)

	Yes	No
• Failure to progress/achieve new milestones	1	0
• Progressive motor deficits	1	0
• Impaired brain growth (acquired microcephaly, or advancing brain atrophy on CT or NMR scan)	1	0

OTHER INFECTIOUS DISEASES:

	Yes	No
• Candidiasis, oral or pharyngeal >2 months or recurrent despite topical therapy	1	0
• Cytomegalovirus infection, with onset BEFORE 1 month of age	1	0
• Herpes stomatitis, 2 or more episodes in 1 yr.	1	0
• HSV bronchitis, pneumonitis, or esophagitis with onset BEFORE 1 month of age	1	0
• Herpes zoster, multidermatomal or disseminated	1	0
• Herpes zoster, single dermatome	1	0
• Disseminated varicella (complicated chickenpox)	1	0
• Nocardiosis	1	0
• Persistent/recurrent otitis media	1	0
• Recurrent/chronic lower respiratory infection of undetermined etiology	1	0
• Congenital syphilis	1	0
• Toxoplasmosis, onset BEFORE 1 month of age	1	0

TUBERCULOSIS:

	Yes	No	Unk.
• Skin tested for tuberculosis (TB)	1	0	9

	Pos	Neg.	Not Done	Unk.	most recent test date Mo./ Yr.
• Test results (most recent test)	1	0	2	9	

	Yes	No	Unk.
• Child has received medications for TB prophylaxis	1	0	9
• Diagnosed with TB disease (supplementary TB form should be completed on patients diagnosed with TB)	1	0	9

OTHER DIAGNOSIS, POSSIBLY HIV-RELATED: (Subclass F)

	Yes	No		Yes	No
• Hepatitis	1	0	• Anemia	1	0
• Cardiomyopathy	1	0	• Thrombocytopenia	1	0
• Nephropathy	1	0	• Dermatitis	1	0

• Other diagnoses, possibly HIV-related: (specify) _____

_____

VII. LABORATORY DATA

HIV SERUM ANTIBODY TESTS: (If several, specify latest)

	Pos	Neg.	Pos/ Oral	Inc*	Not Done	TEST DATE Mo.	TEST DATE Yr.
• ELISA	1	0	2	8	9		
• Western blot/immunofluorescence assay	1	0	2	8	9		
• Other: _____	1	0	2	8	9		

*Inc = Inconclusive

HIV DETECTION TESTS: (record earliest positive results)

	Pos	Neg.	Pos/ Oral	Inc*	Not Done	TEST DATE Mo.	TEST DATE Yr.
• HIV Culture (initial result)	1	0	2	8	9		
• HIV Culture (confirmatory result)	1	0	2	8	9		
• HIV PCR (initial result)	1	0	2	8	9		
• HIV PCR (confirmatory result)	1	0	2	8	9		
• HIV Serum antigen test	1	0	2	8	9		
Other: _____	1	0	2	8	9		

If HIV tests were not positive, were not done, or the patient is <15 months of age, does this patient have an immunodeficiency that would disqualify him/her from the AIDS case definition? Yes 1 No 0 Unk. 9

IMMUNOLOGIC LAB TEST:

	Number	Test Date Mo.	Test Date Yr.
• lymphocyte count, (lowest)			
• T-Helper cell count, (CD4+ cells) (lowest)			
• T-Helper/T-suppressor ratio, (lowest)	.		
• T-Helper percent (CD4 %) (lowest)			
• T-Suppressor cell count (CD8 count) (highest)			
• T-Suppressor percent (CD8 %) (highest)			

	Number	Test Date Mo.	Test Date Yr.
• Total serum immunoglobulins (mg/dL): (highest)			
• Ig G			

VIII. TREATMENT/PROPHYLAXIS DATA

PATIENT NUMBER: ☐☐☐☐☐☐☐☐☐ FORM NUMBER: [0]

TREATMENT/PROPHYLAXIS: (patient has received)

ANTIRETROVIRALS:	Yes	No	P/B*	Unk.
• AZT (Retrovir, ZDV)	[1]	[0]	[2]	[9]
• ddI (dideoxyinosine, Videx)	[1]	[0]	[2]	[9]
• ddC (dideoxycytidine)	[1]	[0]	[2]	[9]
• Other: _____	[1]	[0]	[2]	[9]
• Other: _____	[1]	[0]	[2]	[9]
OTHER ANTIVIRALS:				
• Acyclovir (ACV, Zovirax)	[1]	[0]	[2]	[9]
• Ganciclovir (DHPG)	[1]	[0]	[2]	[9]
• Ribavirin (Virazole)	[1]	[0]	[2]	[9]
• Other: _____	[1]	[0]	[2]	[9]

*P/B = blinded or placebo controlled

IMMUNOMODULATORS:	Yes	No	P/B*	Unk.
• Interferon	[1]	[0]	[2]	[9]
• Long term steroids	[1]	[0]	[2]	[9]
• Immune Globulin IV	[1]	[0]	[2]	[9]
• Other: _____	[1]	[0]	[2]	[9]
PROPHYLAXIS/SUPPRESSIVE TX:				
• TMP-SMX	[1]	[0]	[2]	[9]
• Pentamidine	[1]	[0]	[2]	[9]
• Amphotericin B	[1]	[0]	[2]	[9]
• Dapsone	[1]	[0]	[2]	[9]
• Fluconazole (Diflucon)	[1]	[0]	[2]	[9]
• Other: _____	[1]	[0]	[2]	[9]

IMMUNIZATIONS GIVEN:

	Any doses? Yes	No	Unk.	Total no. of doses	Last dose Mo.	Yr.
• Measles	[1]	[0]	[9]	☐☐	☐☐	☐☐
• Varicella	[1]	[0]	[9]	☐☐	☐☐	☐☐

	Any doses? Yes	No	Unk.
• Bacillus Calmette-Guerin	[1]	[0]	[9]

IX. SOCIAL DATA

CHILD'S CURRENT PRIMARY CARETAKER:

[1] Biologic parent(s) [2] Other relatives
[3] Foster parents, relative [4] Foster parents, unrelated
[5] Adoptive parents, relative [6] Adoptive parents, unrelated
[7] Social service agency [8] Other: _____

CHILDS SCHOOL ATTENDANCE (K and above):

[0] Not receiving education [1] Attending outside home
[2] Home tutor [3] Too young to attend school
[9] Unknown

MOTHER'S CURRENT STATUS [1] Alive [2] Dead [9] Unk.

SIBLINGS:

	Total	Older:	Younger:
• Number of siblings by mother	☐☐	☐☐	☐☐
• Number diagnosed with HIV infection or AIDS	☐☐	☐☐	☐☐ (99 = unk.)

MAIN REIMBURSEMENT SOURCE: (check one)

[1] Medicaid [2] Private insurance/HMO
[3] No coverage [4] Other public funding
[7] Clinical Trial/government program (listed below)
[9] Unknown

THIS CHILD/FAMILY HAS BEEN REFERRED FOR SOCIAL SERVICE SUPPORT:

[1] Yes, referred by health department [2] Yes, referred by health care/other provider
[3] No, family refused referral [4] No
[9] Unknown

THIS PATIENT HAS BEEN ENROLLED AT: (check all that apply)

Clinical Trial:	Clinic:
[1] NIH -- sponsored	[1] HRSA -- sponsored
[2] Other	[2] Other
[3] None	[3] None
[9] Unknown	[9] Unknown

X. DATA COLLECTION SOURCES

COLLECTION SOURCES: (check all that apply)

	Yes	No
• HIV Specialty clinic chart	[1]	[0]
• Inpatient record from reporting hospital	[1]	[0]
• Other outpatient records from reporting hospital	[1]	[0]
• Record from other hospital	[1]	[0]
• Non-hospital clinic/Private physician chart	[1]	[0]
• Medical or social service agency: (specify) _____	[1]	[0]
• Other: _____	[1]	[0]

SOURCE OF REPORT: (Source of initial report that led to identification of child to PSD project)

	Code
• Infection Control Practitioner	[1]
• HIV Clinic/Rx Trial/Hemophilia Clinic	[2]
• Sentinel Physician/Clinic referral	[3]
• Maternity/Prenatal Care	[4]
• Nursery	[5]
• HIV Testing Site	[6]
• Record Review	[7]
• Social Services	[8]
• Other: _____	[9]

XI. ADDITIONAL INFORMATION OR COMMENTS

_____

_____

_____

_____

PEDIATRIC HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION: INITIAL FORM (00) (revised 05/30/03)

HARSO: | COMPLETED/ABSTRACTED DATE: mm dd yy | ENROLLMENT DATE: mm dd yy | DATE OF INITIAL PSD SITE CONTACT FOR THIS CHILD: mm dd yy

I. BASIC PATIENT INFORMATION

PATIENT NUMBER: | DATE OF BIRTH: mm dd yy | SOUNDEX NAME CODE: | HEALTH DEPARTMENT: State City/County | SEX: 1 Male 2 Female

ETHNICITY Check one:
1 Hispanic or Latino 2 Not Hispanic or Latino 9 Unknown

RACE Check all that apply:
1 White 2 Black/African American 5 American Indian/Alaska Native
6 Asian 7 Hawaiian Native/Other Pacific Islander 8 Other:_____
9 Not specified

HOSPITAL WHERE DIAGNOSIS OF HIV CONSIDERED:
Name_____
State:_____ City_____

COUNTRY OF BIRTH:
1 U.S. 2 U.S. Dependencies/Possessions (including Puerto Rico) (specify):_____
8 Other specify):_____ 9 Unknown

FOR PERINATAL CASES:

	Yes	No	Unknown
Was mother diagnosed with HIV (or AIDS) before child's birth?	1	0	9
Did mother have HIV symptoms at the time of child's birth?	1	0	9
Did mother have prenatal care?	1	0	9

REASON FOR INITIAL EVALUATION Check all that apply:

	Yes	No	Unknown
Child had potential exposure to HIV	1	0	9
Child had symptoms suggestive of HIV	1	0	9
Found in routine screening	1	0	9

RESIDENCE AT DIAGNOSIS OF HIV INFECTION/EXPOSURE: State _____ City_____
County_____ Zip _____ Country

DATE OF INITIAL EVALUATION FOR HIV INFECTION mm dd yy

This child's biologic mother had: (check all that apply)

	Yes	No	Unknown
Injected nonprescription drugs	1	0	9
Heterosexual relations with:			
Person who injected nonprescription drugs	1	0	9
Bisexual man	1	0	9
Male with hemophilia/coagulation disorder	1	0	9
Transfusion recipient with documented HIV infection	1	0	9
Transplant recipient with documented HIV infection	1	0	9
Male with documented perinatal HIV infection	1	0	9
Male with AIDS or documented HIV infection, risk not specified	1	0	9
Received a transfusion of blood/blood components (other than clotting factor)	1	0	9
Received transplant of tissue/organs or artificial insemination	1	0	9
Been diagnosed as having AIDS or documented HIV infection	1	0	9
If yes, was this mother perinatally HIV-infected?	1	0	9
Other (specify)_____	1	0	9

Before the diagnosis of HIV infection this child had: (check all that apply)

	Yes	No	Unknown
Received clotting factor for coagulation disorder?	1	0	9
If yes, specify: 1 Factor VIII (Hemophilia A) 2 Factor IX (Hemophilia B) 8 Other: specify_____	1	0	9
Received a transfusion of blood/blood components (other than clotting factor)	1	0	9
FIRST mm/dd/yy LAST mm/dd/yy			
Received transplant of tissue/organs	1	0	9
Sexual contact with a male	1	0	9
Sexual contact with a female	1	0	9
Injected nonprescription drugs	1	0	9
Been breastfed	1	0	9
If yes, duration.....Enter number _____ 1 days 2 months 9 unknown			
Other (specify)_____	1	0	9

PERINATAL CASES ONLY:

Is this child's mother enrolled in PSD? Yes 1 No 0 Unknown 9 If yes, enter mother's PSD number: Site _____ Patno _____

Mother's date of birth mm dd yy Mother's age at delivery _____ years

MOTHER WAS BORN IN:
1 U.S. 2 U.S. Dependencies and Possessions (including Puerto Rico) (specify):_____
8 Other specify):_____ 9 Unknown

FATHER WAS BORN IN:
1 U.S. 2 U.S. Dependencies and Possessions (including Puerto Rico) (specify):_____
8 Other specify):_____ 9 Unknown

ETHNICITY OF MOTHER Check one:
1 Hispanic or Latina 2 Not Hispanic or Latina 9 Unknown

ETHNICITY OF FATHER Check one:
1 Hispanic or Latino 2 Not Hispanic or Latino 9 Unknown

RACE OF MOTHER Check all that apply:
1 White 2 Black/African American 5 American Indian/Alaska Native
6 Asian 7 Hawaiian Native/Other Pacific Islander 8 Other:_____
9 Not specified

RACE OF FATHER Check all that apply:
1 White 2 Black/African American 5 American Indian/Alaska Native
6 Asian 7 Hawaiian Native/Other Pacific Islander 8 Other:_____
9 Not specified

OTHER INFORMATION ON MOTHER Check all that apply:

	Yes	No	Unknown
History of crack use	1	0	9
History of other street drug use (non IV)	1	0	9
Has mother received payment or drugs for sex?	1	0	9

Information in the surveillance system that would permit identification of any individual on whom a record is maintained, is collected with a guarantee that it will be held in confidence, will be used only for the purposes stated in the assurance in the protocol, and will not otherwise be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 USC 242m).

INITIAL FORM - Continued PATIENT NUMBER ☐☐☐☐☐☐☐☐☐☐ FORM NUMBER 00

II. BIRTH HISTORY: Hospital: _____ City: _____ State ☐☐ Birth weight: ☐☐☐☐ grams

Type:	Delivery:	Gestational age:	Withdrawal symptoms:	Urine toxic screen:	Nursery stay:	Chronic underlying disease: (ICD9 code)
1 Single 2 Twin 3 Triplet 4 Other Specify ___ 9 Unknown	1 Vaginal 2 Caesarean 9 Unknown	1 Full-term 2 Premature ☐☐ Weeks (99 = Unk)	1 Yes 0 No 9 Unknown	1 Positive 0 Negative 2 Not done 9 Unknown	1 < 7 days 2 7-30 days 3 > 30 days 9 Unknown	☐☐☐☐☐ _____

If Cesarean section, was it elective? 1 Yes 0 No 9 Unknown

Indication for Cesarean section (check all that apply)
1 HIV indication 2 Fetal distress 3 Previous C-section (repeat)
4 Placenta abruptia/previa 5 Malpresentation (breech, transverse lie) 6 Prolonged labor/failure to progress
8 Other (Herpes, disproportion, etc) Specify _____ 9 Not specified

Mother's reproductive history *including this pregnancy and before the birth of this child:*
Gravida (number of pregnancies) ☐☐ Number of spontaneous miscarriages/stillbirths ☐☐
Para (number of live births) ☐☐ Number of elective or induced abortions ☐☐ *OR* Total number of spontaneous/induced abortions ☐☐

Date and time of birth-related events:
Admission to labor and delivery..... ☐☐:☐☐ (military time-24° clock) ☐☐/☐☐/☐☐ mm/dd/yy Unknown ☐
Onset of labor..... ☐☐:☐☐ (military time-24 ° clock) ☐☐/☐☐/☐☐ mm/dd/yy Unknown ☐
Duration of labor..... ≥ ☐ ☐☐:☐☐ (hours/minutes) Check ≥ if exact hours and minutes are not recorded
Rupture of membranes..... ☐☐:☐☐ (military time-24° clock) ☐☐/☐☐/☐☐ mm/dd/yy Unknown ☐
Duration of rupture of membranes..... ≥ ☐ ☐☐:☐☐ (hours/minutes) Check ≥ if exact hours and minutes are not recorded.
Delivery..... ☐☐:☐☐ (military time-24° clock) Unknown ☐
Infant began prophylactic antiretroviral(s)..... ☐☐:☐☐ (military time-24° clock) ☐☐/☐☐/☐☐ mm/dd/yy Unknown ☐

Complications related to childbirth: Check all that apply.

- *Infant complications as a result of Cesarean delivery:* 0 None 8 Not applicable 9 Unknown
  - 1 Lacerations (accidental, complicating delivery) [767.8]
  - 2 Neonatal depression (maternal anesthesia) [763.5]
  - 3 Transient tachypnea of the newborn (TTN) [770.6]
  - 6 Unspecified complication [763.4] (excludes placental separation or hemorrhage from Cesarean section) fetus or newborn affected by other complications of labor and delivery: Cesarean delivery
  - 7 Other specified complications Specify _____ ICD9 code _____
- *Infant complications as a result of vaginal delivery:* 0 None 8 Not applicable 9 Unknown
  - 1 Birth trauma [767, 767.0-767.9]
  - 2 Fetal distress [768.2-768.4]
  - 3 Shoulder dystocia [660.4]
  - 4 Transient tachypnea of the newborn (TTN) [770.6]
  - 6 Unspecified complication of labor and delivery affecting fetus or newborn [763.9]
  - 7 Other specified complications Specify _____ ICD9 code _____[e.g.763.82, 763.83, 763.89]
- *Maternal complications as a result of Cesarean or vaginal delivery* 0 None 9 Unknown
  - 01 Amnionitis [658.4]
  - 02 Amniotic fluid embolism [673.1]
  - 03 Deep vein thrombosis [671.4]
  - Hemorrhage: 04 Antepartum hemorrhage, maternal blood loss [641.1-8]
  - 05 Postpartum hemorrhage (puerperal hemorrhage) [666.1]
  - 06 Cesarean section wound hemorrhage [674.3]
  - 07 Surgical procedure [998.11]
  - 10 Hemorrhage complicating delivery – unspecified [641.9]
  - 11 Inversion of uterus [665.2]
  - 12 Postpartum endometritis [646.6]
  - 13 Pyelonephritis [590.0-590.1]
  - 14 Septic pelvic thrombophlebitis [671.4]
  - 15 Urinary tract infection [599.0, 646.6, 646.5]
  - 16 Wound infection [998.59]
  - 17 Other specified complications Specify _____ ICD9 code _____

Mother received antiretroviral medications during pregnancy *not including labor and delivery?* 1 Yes 0 No 9 Unknown

If yes, what week/trimester of pregnancy was antiretroviral medication started: Weeks ☐☐ (99=unknown) *or* Trimester 1 2 3

If yes, list drug codes

Regimen #1 1 ☐☐☐☐ 2 ☐☐☐☐ 3 ☐☐☐☐ 4 ☐☐☐☐ 5 ☐☐☐☐ 6 ☐☐☐☐

Regimen #2 1 ☐☐☐☐ 2 ☐☐☐☐ 3 ☐☐☐☐ 4 ☐☐☐☐ 5 ☐☐☐☐ 6 ☐☐☐☐

Mother received antiretroviral medications during labor and delivery? 1 Yes 0 No 9 Unknown If yes, list drug codes

Drug codes 1 ☐☐☐☐ 2 ☐☐☐☐ 3 ☐☐☐☐ 4 ☐☐☐☐ 5 ☐☐☐☐ 6 ☐☐☐☐

Is mother noted to be resistant to any antiretroviral medications? 1 Yes 0 No 9 Unknown If yes, list drug codes

Drug codes 1 ☐☐☐☐ 2 ☐☐☐☐ 3 ☐☐☐☐ 4 ☐☐☐☐ 5 ☐☐☐☐ 6 ☐☐☐☐

Drug codes 7 ☐☐☐☐ 8 ☐☐☐☐

III. SOURCE OF REPORT

- Infection Control Practitioner..... 1
- HIV Clinic/Rx Trial/Hemophilia Clinic..... 2
- Sentinel Physician/Clinic referral..... 3
- Maternity/Prenatal Care 4
- Nursery 5
- HIV Testing Site..... 6
- Record Review 7
- Social Services..... 8
- Other _____ 9

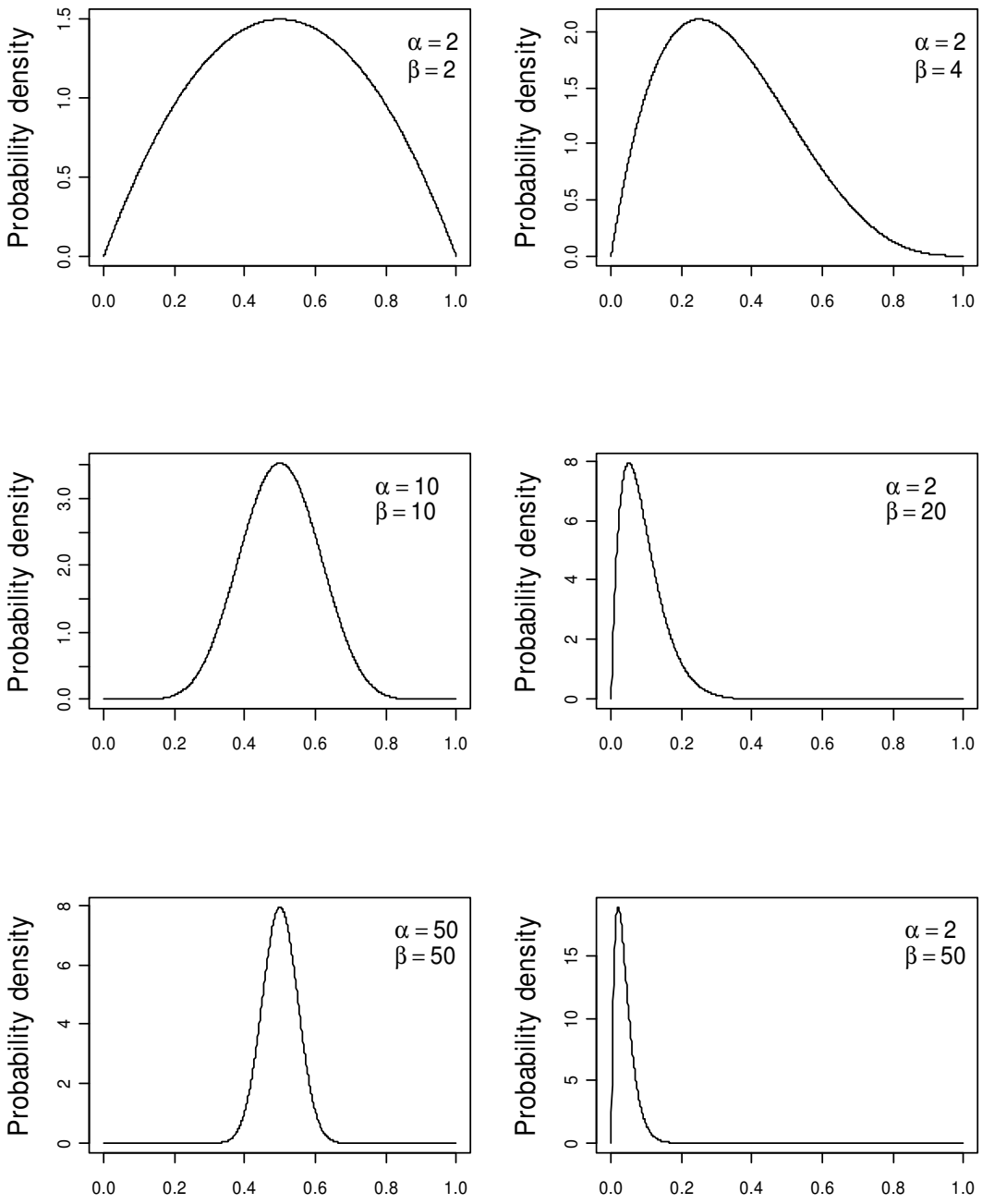
Appendix 5 The beta distribution

The beta distribution is a continuous probability distribution with range bounded between 0 and 1. It is defined in terms of two shape parameters, α and β, where α can be interpreted as the number of subjects within a group that experience an event, and β as the number who do not experience an event (Lynd & O'Brien, 2004). The mean of the distribution is therefore α / (α+β), and its standard deviation is

$$\sigma = \sqrt{\frac{\alpha \times \beta}{(\alpha + \beta)^2 (\alpha + \beta + 1)}}$$

Beta probability density functions may be asymmetric and have different shapes to normal ones (e.g. they may be flatter, more peaked, or more concentrated around the mean than a normal distribution). Figure A.5 shows examples of the diverse beta probability densities that can be generated by varying the values of α and β.

Figure A.5 Examples of beta distributions



Appendix 6 Methods for calculating prematurity-specific mother-to-child transmission rates

Equations were derived as follows, with *R* corresponding to 'risk', and *B* to 'benefit'.

	Uninfected	Infected	Total
Term	a	b	$a+b$
Premature	c	d	$c+d$
Total	$a+c$	$b+d$	n

Given the above table, the prematurity rate is $R_0 = \frac{c+d}{n}$ which means that $c+d = R_0 \times n$. The MTCT rate is $B_0 = \frac{b+d}{n}$, which means that $b+d = B_0 \times n$, and $d = (B_0 \times n) - b$. If RR is the relative risk of transmission in the term group compared with the premature group, then $RR = \frac{d/(c+d)}{b/(a+b)} = \frac{d \times (a+b)}{b \times (c+d)}$. Although a, b, c and d are not known, $c+d$ can be substituted with $R_0 \times n$, $a+b$ with $(1-R_0) \times n$, and d with $B_0 \times n - b$, giving:

$RR = \frac{(B_0 \times n - b) \times (1-R_0) \times n}{b \times n \times R_0}$, which simplifies to $RR = \frac{(B_0 \times n - b) \times (1-R_0)}{b \times R_0}$.

Solving this equation for *b* gives $b = \frac{B_0 \times n \times (1-R_0)}{RR \times R_0 + (1-R_0)}$.

The transmission rate in the term group, B_t, is $\frac{b}{a+b}$. Substituting b from above, and $a+b$ with $(1-R_0) \times n$, gives:

$$B_t = \frac{B_0}{RR \times R_0 + (1-R_0)} \qquad \text{Equation 3}$$

and

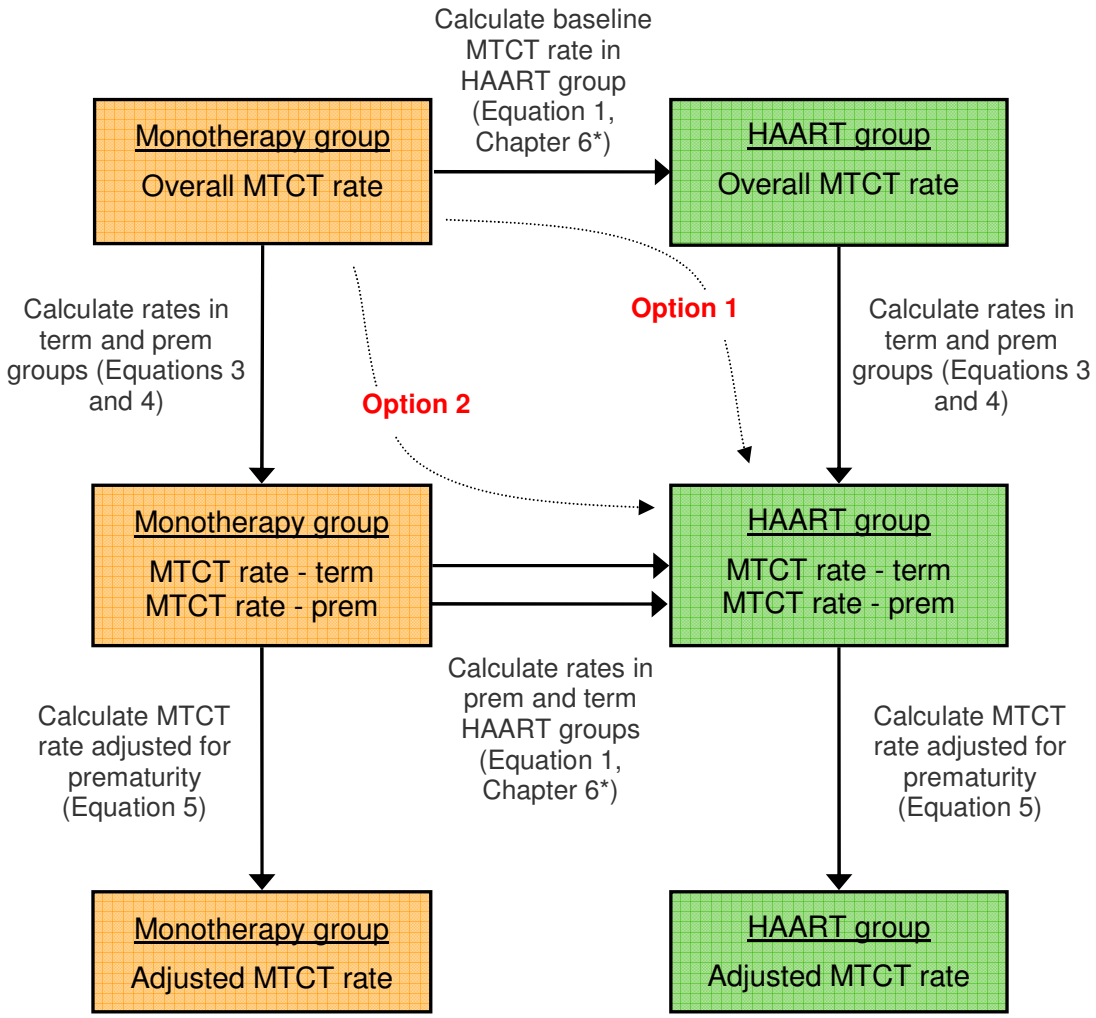
$$B_p = RR \times B_t \,. \qquad \text{Equation 4}$$

For each simulation of the monotherapy scenario, a mother-to-child transmission (MTCT) rate $(\hat{B}_0)$ was sampled; $\hat{B}_t$ and $\hat{B}_p$ were then calculated using Equations 3 and 4, with R_0 equal to the population prematurity rate. A sampled prematurity rate, $\hat{R}_0$, was then obtained, and the transmission rate was adjusted by taking a weighted average of the term and premature transmission rates, as follows:

$$\hat{B}_0 = (\hat{B}_p \times \hat{R}_0) + (\hat{B}_t \times (1 - \hat{R}_0)) \qquad \text{Equation 5}$$

For the highly active antiretroviral therapy (HAART) scenario, there were two options for adjusting for the association between transmission and prematurity (shown in Figure A.6), which yield slightly different results. Option 1 was chosen, as this method meant that the adjusted odds ratio for MTCT in the HAART group was applied to the overall MTCT rate in the monotherapy group, rather than to the MTCT rates specific to term or premature infants. This scenario is closer to the original data, and avoids making the assumption that the association between treatment and MTCT is independent of prematurity.

Figure A.6 Diagram showing two different ways of adjusting for the association between prematurity and mother-to-child transmission (MTCT)



HAART, highly active antiretroviral therapy; MTCT, mother-to-child transmission; prem, premature.

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